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Archives of Internal Medicine

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STUDIES ON THE VISCERAL NERVOUS SYSTEM

ON THE REFLEX CONTROL OF THE PYLORUS *

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CHICAGO

It occurred to us that the device used in the study of the reflex control of the cardia and lower esophagus [1] might be adapted to a similar study of the pylorus, and, for acute experiments on anesthetized animals, might possibly present less local trauma, irritation and abnormal conditions than were involved in previous work on the pylorus, excepting the use of the roentgen ray on man and animals not under anesthesia.

The mechanism of pylorus control has challenged numerous investigators in recent years, partly from physiologic interest, partly because of the importance of the pylorus in the motor and secretory disturbances of the stomach. As regards local mechanism involving only the pylorus and adjacent regions of the antrum and upper duodenum, Cannon,[2] in 1904, summarized his own observations and those of previous investigators in his theory of "acid control of the pylorus," that is, the acid of the gastric juice acting on the stomach side of the pylorus opens the pylorus, while acid on the duodenal side closes the pylorus, both actions being primarily local reflexes. The part of the theory stating that acid, acting on the stomach side, opens the pylorus, has not been substantiated by subsequent investigations, largely by methods different from Cannon's. Thus Morse reports that water leaves the stomach faster than acid, and weak acids leave the stomach faster than strong acids. Cowie and Lyon,[3] working on infants, found that rendering the food either acid or alkaline delays gastric evacuation. They also maintain that free acid in the stomach is not necessary for pyloric relaxation and initial gastric evacuation. Spencer [4] and others, working on adult persons, reach essentially the same conclusions and report specifically that rendering the food alkaline hastens the emptying of the stomach. McClure [5] and others, working with the roentgen ray on adult persons, report that a mixed, well masticated meal starts to pass through the

* From the Hull Physiological Laboratory of the University of Chicago.

1. Carlson, Boyd and Pearcy: Am. J. Physiol. **61**:14, 1922.
2. Cannon: Mechanical Factors of Digestion, 1911, p. 96.
3. Cowie, D. M., and Lyon, W.: Further Observations of the Acid Control of the Pylorus in Infants, Am. J. Dis. Child. **2**:252 (Oct.) 1911.
4. Spencer: Am. J. Physiol. **39**:459, 1916.
5. McClure, C. W.; Reynolds, L., and Schwartz, C. O.: On Behavior of Pyloric Sphincter in Normal Man, Arch. Int. Med. **26**:410 (Oct.) 1920.

pylorus a few minutes after eating begins, and that introducing acids in the duodenum does not essentially modify the rate of the evacuation. Luckhardt and Carlson [6] found (in man, and dog) that opening of the pylorus and the passing of the gastric contents into the duodenum was correlated with the periodic tonus rhythm of the stomach rather than with the variations in gastric acidity.

It needs scarcely be pointed out that the rate of evacuation of the stomach cannot be used as a direct measure of pylorus tonus, because, except in cases of pathologic pylorospasm or mechanical narrowing of the pyloric orifice, the emptying rate of the stomach depends on the motility of the stomach and the reflex state of the duodenum, as well as on the tonus of the pylorus. On the other hand, most observers agree that mechanical or chemical irritation of the duodenal mucosa induces spasms of the duodenum, regurgitation of duodenal contents into the stomach and pyloric contraction or spasm of varying duration.

The control of the pylorus by extrinsic reflex mechanism involves first of all a consideration of the path and character of the efferent nerves of this region. There are some seeming contradictions between the individual reports on this phase. The literature is reviewed in the recent paper by Thomas and Wheelon.[7]

Thomas and Wheelon, working on the anesthetized dog, introduced a specially constructed enterograph into the antrum, pylorus and upper duodenum. This apparatus consisted of three separate chambers in a solid rubber case, the chambers being covered with thin rubber. The apparatus was adjusted so as to give separate records of the antrum, pyloric and duodenal contractions. By means of this device they report rhythmic contractions of the pylorus (from three to five per minute), contraction and inhibition of the pylorus on stimulation of the peripheral ends of both the vagus and the splanchnic nerves, but only an inhibitory action on the pylorus by epinephrin. They conclude that the vagi as well as the splanchic nerves carry motor and inhibitory fibers to the pyloric sphincter.

The enterograph of Thomas and Wheelon is straight and in the transverse diameter unyielding or rigid at four points. The apparatus was fixed in place by sutures through the antrum. It would seem that the rigidity of the apparatus introduces serious abnormal conditions and local irritations, especially when there is marked tonus and contractions of regions about the apparatus.

Few studies appear to have been made on the extrinsic reflex control of the pylorus. Barber and Stewart,[8] in a preliminary note, have described a diffuse pylorospasm in dogs, with a fundic relaxation fol-

6. Luckhardt, Phillips and Carlson: Am. J. Physiol. **50**:57, 1919.
7. Thomas and Wheelon: J. Lab. & Clin. Med. **7**:3, 1922.
8. Barber and Stewart: Proc. Soc. Exper. Biol. & Med. **17**:155, 1920.

lowing irritation of the gallbladder, the appendix and the duodenum. They report that this pylorospasm disappears on irritation of the parietal peritoneum. The method of recording or observing these reflexes into the pylorus are not described.

METHODS

The experimental arrangements are shown by the diagram in Figure 1. The pyloric condom balloon (*C*) with the retention plug (*D*) may, for the sake of brevity, be called a "pylorometer." For construction and size of this contrivance the reader is referred to our report on innervation and reflex control of the cardia.[1] It is obvious that if the tonus of the cardia exceeds the air pressure in the tube system *E*, the portion of the delicate balloon (*C*) in the pyloric region will remain collapsed, and manometer *A* will record no pressure variations in the

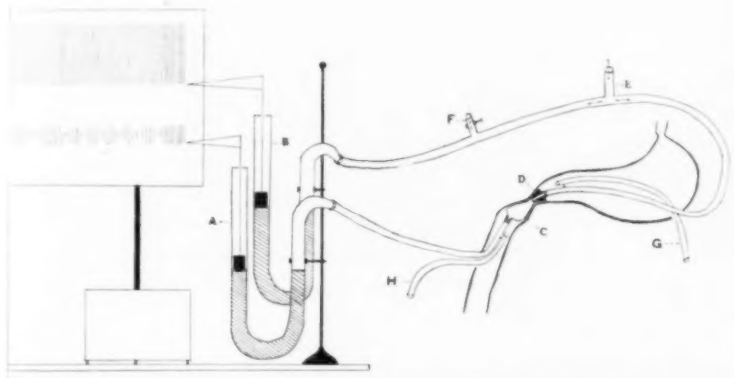

Fig. 1.—Arrangement of contrivances for continuous study of the tonus and contractions of the pylorus in experiments on dogs. *A*, water manometer connecting with the balloon in the pylorus (*C*), and recording the tonus of the pylorus; *B*, control water manometer in the circuit recording possible variations in rate and force of the periodic insufflation of tube *E* with air; *C*, condom balloon in pylorus and upper end of duodenum; *D*, retention plug of the balloon anchored on the antrum side of the pylorus; *E*, rubber tube connecting with a motor driven bellows that provides periodic insufflation of the tube system and pyloric balloon; *F*, outlet tube controlling the degree of the periodic air pressure in the system furnished by the motor driven bellows; *G*, tube serving to introduce fluids into the antrum pylori; *H*, tube serving to introduce fluids into the duodenum.

tube system *E*. The pylorometer was introduced through an opening in the fundus, and anchored in place by the rubber tube attached to the pyloric end of the balloon and by a linen thread attached to the retention plug. Tube and thread were carried out of the duodenum by a small slit in the wall from 8 to 10 cm. below the pylorus. In a few cases the gastrostomy and the duodenostomy were made aseptically two

days before the experiment. In every case from one to one and one-half hours were allowed to elapse after fixing the pylorometer in place and beginning the observation, to eliminate so far as possible abnormal states due to the trauma and mechanical irritation incident to adjusting and recording devices.

Periodic variations in air pressure in the tube system (*E*) were secured by motor driven bellows, with adjustible rate, and volume output. The maximum pressure in the system was further regulated by the size of the aperture, *F*. Manometer *B* served as a control on any accidental variations in the rate and amplitude of air pressure variations in the tube system. Unless the pylorus is extremely atonic, the balloon (*C*) part on the duodenal side of the pylorus does not completely collapse between the positive pressure periods in the tube system. The amount of permanent positive pressure in the manometer *A* is thus a measure of degree of pylorus tonus. The float in the control manometer (*B*) always returns to *O* pressure, owing to the open exit for the air of *F*. But the spasm of the pylorus may be so great that no air can enter the balloon and tube system beyond the pylorus. In this state the method permits the recording of pyloric relaxation only.

The position of the pylorometer was always verified at the end of each experiment.

All the experiments were made on dogs, using barbital anesthesia, or barbital with a trace of ether. In a few experiments ether was used exclusively. Care was taken to keep up the normal body temperature. The dogs were not fed for twenty-four hours prior to experimentation, so as to insure an empty stomach.

For the observations on local reflexes the water, acids and alkalis (at body temperature) were introduced through the rubber tubes, *G* and *H*. These tubes were tied to the pylorometer tube system in the stomach and duodenum so as to insure the contact of the fluid in the pyloric antrum and within a few centimeters of the pylorus on the duodenal side.

RESULTS

1. *Spontaneous Rhythm of the Pylorus.*—Under the conditions of our experiments, the spontaneous motor behavior of the pylorus varied greatly in different animals, and from time to time in the same animal, when observations were continued for from four to six hours. In some cases, the pylorus was in a state of extreme spasm lasting for hours; in other cases, it was completely relaxed and quiescent; but usually the pylorus was in moderate tonus, with periodic variations of tonus. This tonus rhythm may run regularly for hours at a rate of from three to four waves a minute, or the tonus waves may appear more like spasms, the contraction phase lasting for from one to several minutes, with correspondingly long relaxation phases. The regular

and irregular tonus rhythm of the pylorus was also noted by Thomas and Wheelon. Types of the pylorus rhythm as recorded by the present method are shown in Figure 2.

2. *Influence of the Vagi Efferent Fibers on the Pylorus.*—The acute or immediate effects on the pylorus of section of the vagi in the neck or of tetanization of the peripheral end of the cut vagi are variable, but depend in part on the state or condition of the pylorus. The following results may be seen: (1) Section of one or both vagi may have no effect either on the hypertonic (spastic) pylorus or on the atonic pylorus. (2) Section of the vagi may be followed by prolonged relaxation of a hypertonic pylorus and by prolonged contraction of an atonic pylorus. (3) Tetanization of the peripheral end of the cut vagi always induces contraction of the atonic or moderately tonic pylorus, and may cause temporary or prolonged relaxation of the

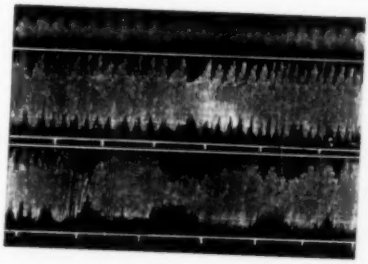

Fig. 2.—Water manometer tracings showing types of spontaneous rhythm of the pylorus in a dog under barbital anesthesia. Time in minutes.

hypertonic or spastic pylorus. Tracings illustrating some of these reactions are reproduced in Figure 3. At no time were the vagi nerves sectioned after prior section of the splanchnic nerves. These results seem to warrant the following interpretation or conclusion.

(*a*) The vagus nerves send both motor and inhibitory efferents to the pylorus.

(*b*) Protracted pylorospasm may in special cases be due to hyperactivity of the vagi motor system, since the spasm may decrease or disappear on section of the vagi.

(*c*) Protracted atonicity may also be due to hyperactivity of the vagi inhibitory efferents, since section of the vagi may increase the tonus of an atonic pylorus.

(d) The vagi inhibitory efferents are, at least in some cases, able to counteract a pylorospasm caused by other than vagi factors, since a spastic pylorus may be relaxed by tetanization of the peripheral end of the cut vagi.

We realize that these interpretations are not free from objections. Since the vagi efferents act also on the entire stomach, and possibly on the duodenal motor mechanisms, it is possible that some of the vagi effects on the pylorus outlined above in reality may be indirect effects from altered motor states of the stomach or duodenum. It is also possible that some of the immediate or temporary effects on the pylorus

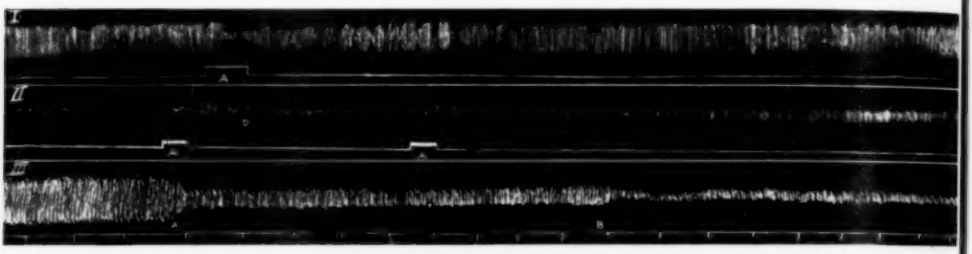

Fig. 3.—Water manometer tracings of a dog under barbital anesthesia. Time in minutes. *Ia*, weak tetanization of peripheral end of the left vagus nerve in the neck, showing temporary tetanus of the pylorus followed by rhythmic contraction; *IIa*, pylorus in spasm, weak tetanization of the peripheral end of the vagus nerve in the neck, showing relaxation of the pylorus on vagus stimulation; *III*, atonic pylorus; *a*, section of the right vagus nerve; *b*, section of the left vagus nerve in the neck, showing increased tonus of the pylorus following section.

following section of the vagi in the neck are not due to section of motor and inhibitory efferents to the pylorus but to mechanical stimulation of vagi afferents and a reflex to the pylorus via the splanchnic efferents.

3. Influence of the Splanchnic Efferent Fibers on the Pylorus.—If the pylorus is atonic or in moderate tonus only, stimulation of the

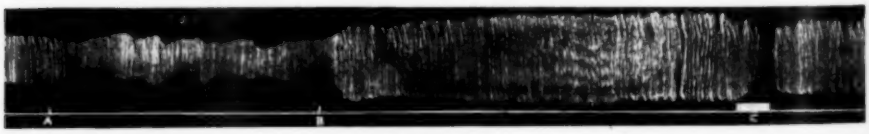

Fig. 4.—Water manometer tracing of a dog under barbital anesthesia. *a*, beginning isolation of the left splanchnic nerves. *b*, section of the left splanchnic nerves; *c*, tetanization of the peripheral end of the left splanchnic nerves, showing tonic motor control of the splanchnic nerves on the pylorus.

peripheral end of the cut splanchnic nerves induces a marked contraction of the pylorus (Fig. 4, *c*). It seems more difficult to secure clear inhibition of the pylorus or splanchnic stimulation, even when the pylorus at the time is hypertonic, but we have occasionally noted such inhibition. Our results are thus in complete agreement with those of

Thomas and Wheelon. The pylorus receives motor and inhibitory efferents both from the vagi and the splanchnics. The extrinsic efferent nerve supply to the pylorus and to the cardia is therefore identical both in character and source.[1]

We have also occasionally noted marked relaxation of the hypertonic or moderately tonic pylorus following the section of one pair of splanchnic nerves (Fig. 4, *b*). This shows that in special cases hypertonus and spasm of the pylorus may be due to excess action of the splanchnic motor efferents.

4. *Reflexes into the Pylorus from Stimulation of Visceral Sensory Nerves.*—(1) Mechanical or electrical stimulation of any visceral afferent nerve may induce a temporary spasm of the pylorus. We have thus obtained contractions of the pylorus by pressing on, rub-

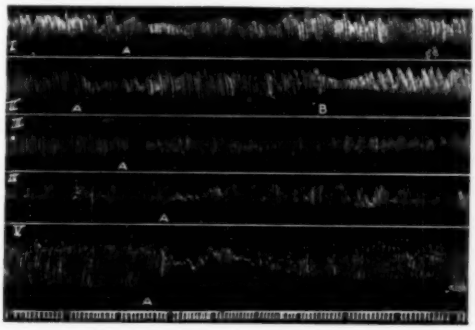

Fig. 5.—Water manometer tracings of a dog under barbital anesthesia. Time in seconds. I*a*, pressing on the wall of the urinary bladder; II*a*, rubbing the parietal peritoneum; *b*, traction on the ureters; III*a*, pressing the large intestine between the fingers; IV*a*, pressing the left kidney between the fingers; V*a*, stretching the rectum by forceps through the anus. Showing reflex contraction of the pylorus by mechanical manipulation of the abdominal viscera.

bing, stretching or crushing the following organs: urinary bladder, ureters, kidneys, large and small intestines, mesentery and parietal peritoneum. Since all of these reflexes into the pylorus persist after section of both vagi in the neck, it is evident that main efferent paths are in the splanchnic nerves. Stretching the anal sphincter or the rectum also causes a temporary pylorospasm (Fig. 5). So far we have not seen an inhibitory reflex into the pylorus from stimulation of visceral afferent nerves. The pylorospasms induced by these visceral irritations and traumas were always temporary, but they may outlast the stimulus by many minutes. We have not tried to elicit these pyloric reflexes after section of the splanchnic nerves or excision of the suprarenal gland to eliminate possible increased output of epinephrin as a

factor in the pylorospasm. It will be remembered that epinephrin induces contraction of the pylorus. This we confirmed on the dog.

It is thus clear that the pylorus and the cardia stand in the same reflex relation to the afferent nerves of the abdominal viscera [1]: The predominant reflexes from the viscera into these sphincters, under our experimental conditions, is motor, and if prolonged they become cardiospasms and pylorospasms.

5. *Reflexes into the Pylorus from Stimulation of Spinal Sensory Nerves.*—Tetanization of the central end of the sciatic nerve produces a temporary spasm of the pylorus (Fig. 6), even after section of both vagus nerves. In two experiments the sciatic stimulation induced relaxation of a spastic pylorus. Occasionally tetanization of the sciatic nerve induces a primary contraction of the pylorus followed by a marked but temporary depression of the tonus of the pylorus.

6. *Reflexes into the Pylorus from the Gastric and the Duodenal Mucosa.*—In this phase of the work we were primarily interested in

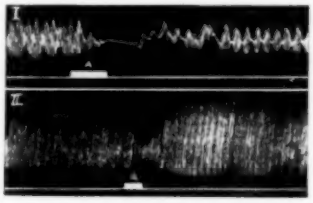

Fig. 6.—Water manometer tracings of a dog under barbital anesthesia. I, strong tetanization of central end of sciatic nerve, showing tetanus of the pylorus followed by hypertonus; IIa, moderately strong tetanization of the central end of the sciatic nerve, showing increased tonus of the pylorus followed by relaxation.

determining to what extent the findings of previous investigators could be confirmed by these new experimental methods. Unless the pylorus is already in hypertonus or spasm, one never fails to secure contractions of the pylorus from anything and everything that stimulates the nerve endings in the duodenal mucosa. This pylorus reflex is induced by rubbing the duodenal mucosa with a probe, or a rubber tube, by slowly introducing from 5 to 10 c.c. of water, weak acids or weak alkalis (Fig. 7). The pylorospasm induced by acid and alkalis in the duodenum is more marked than that induced by water in the duodenum. The stronger the acid or alkali, the stronger and the more prolonged is the pylorospasm.

These observations merely confirm those of previous investigators, beginning with Pavlov's pupil, Serdjukow. But we see no justification for calling this reaction an "acid reflex" specifically, since everything

Fig. 7.—Water manometer tracings in a dog under barbital anesthesia. Ten c.c. quantities of water, hydrochloric acid (0.1 per cent. and 0.2 per cent.), and sodium carbonate (0.2 per cent.) into duodenum, showing reflex contraction of the pylorus from any fluid put into the duodenum.

capable of stimulating the local nerve endings produces the reflex. We ordinarily do not call the retraction of the leg of the frog on irritating the skin of the toes with acids an "acid reflex."

If these duodenal nerve endings are hyperirritable, as in an ulcer region, they may be continuously stimulated not only by water and by acid or neutral gastric content, but also by the alkaline bile and pancreatic juice, and hence a more or less continuous pylorospasm may be induced.

It was shown by Brunemeier and Carlson[9] (1915) that the stimuli in the duodenum that call forth contraction of the pylorus, induce at the same time (and by local reflex mechanisms) inhibition of the tonus and contractions of the empty stomach. Those who seek for teleologic relations may therefore call this a "protective reflex," the "gate" being shut and the driving power of the stomach reduced so that for a while at least no more irritating material enters the duodenum.

Under our experimental conditions water, acids (up to 0.2 per cent. hydrochloric acid) or alkalis acting on the antrum mucosa had no effect on the tonus of the pylorus. This is true whether the pylorus was in hypertonus and spasm, in moderate tonus or atonic. These substances acting in the stomach caused neither relaxation nor contraction of the pylorus.

Our results, therefore, offer no support to the theory that acids acting on the antrum mucosa relaxes the pylorus. But negative results in animals under anesthesia do not necessarily refute positive findings by means of the roentgen-ray method on animals not under anesthesia. It seems, however, that our preparations should be no more abnormal than the excised and anemic stomach kept in oxygenated Ringer's solution, and Cannon has reported that acids on the stomach side open the pylorus in such preparations.

SUMMARY

A new method of accurate and continuous recording of the tonus and contractions of the pylorus is described, a method that seems to involve the minimum of local trauma consistent with accurate graphic recording. By this method on dogs under general anesthesia we find that:

Motor and inhibitory nerve fibers enter the pylorus by way both of the vagi and of the splanchnic nerves (confirming previous observers).

There are types of pylorospasm that may be decreased or removed by (*a*) section of the vagus nerves, (*b*) by section of the splanchnic nerves, (*c*) by stimulation of the peripheral end of these nerves. There are states of atonicity of the pylorus that may be relieved by section

9. Brunemeier and Carlson: Am. Jour. Physiol. **36**: 191, 1915.

of the vagus nerves. These facts indicate that states of spasm or atonicity of the pylorus may be caused by excess activity of either the vagus or the splanchnic efferents, motor and inhibitory.

Appropriate stimulation of all visceral sensory, and at least some spinal sensory (sciatic, sacral), nerves induces a temporary contraction or spasm of the pylorus. The vagus nerves are not necessary for this reflex.

Mechanical or chemical water, hydrochloric acid and sodium carbonate irritation of the duodenal mucosa causes contraction of the pylorus. It does not seem justified to designate this specifically as an "acid reflex." These stimuli, acting in the antrum under the same experimental conditions, do not influence the motor state of the pylorus.

Motor disturbances of the pylorus may thus be induced not only by local pathologic condition in the stomach and duodenum, or by abnormal states of the central nervous system, but also by excessive irritation of most, if not all, sensory nerves, particularly those of the abdominal viscera.

As a working hypothesis, the view is advanced that the action of visceral efferents (sympathetic and autonomic), at least on some of the motor mechanisms, are association or reflex responses and not simple peripheral responses like that of the skeletal muscles on stimulation of the pyramidal tract. That is, the visceral efferents are in reality afferents to local but diffuse reflex mechanism in the viscera. The prevailing view of simple antagonistic action of the vagus and the sympathetic systems is not tenable for the cardia, the stomach and the pylorus. Motor or inhibitory effects on these regions of the intestine are produced by both the vagi and the splanchnic systems, the character of the peripheral response depending on the initial physiologic state of the peripheral motor mechanism, analogous to the so-called "postural reflexes" of the spinal-skeletal system.

A COMPARISON OF NORMAL STANDARDS FOR THE VITAL CAPACITY OF THE LUNGS OF WOMEN*

RUTH E. BOYNTON, M.D.

MINNEAPOLIS

Since the invention of the spirometer by John Hutchinson [1] in 1846, many valuable observations have been made by him and numerous other investigators on the vital capacity of the lungs in normal persons, as well as in those suffering from disease.

I shall not give a complete review of the literature on this subject, but references to certain important and closely related contributions will be given.

It is now an accepted fact that the vital capacity of a person is reduced in certain diseased conditions of the lungs, pleura and heart. The observations of Myers,[2] Garvin, Lundsgaard and Van Slyke,[3] Ulrich and Nathanson,[4] Wittich, Myers and Jennings,[5] Peabody and Wentworth,[6] Dreyer and Burrell [7] and others have shown that there is a definite relation between the vital capacity of the lungs and the amount and type of the pathologic condition of the thoracic organs. Their studies also show that the vital capacity readings are an aid in rendering prognosis and in guiding a patient's activities.

This recognition of the value of vital capacity readings in clinical medicine has renewed the interest of investigators to determine satis-

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*Read before the combined staffs of Lymanhurst School and Parkview Sanatorium, Minneapolis, June 26, 1923.

*From the Students' Health Service and the Department of Preventive Medicine and Public Health of the Medical School, University of Minnesota.

1. Hutchinson, John: On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Medico-Chir. Trans. **29,** 1846.

2. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease. IV. A Comparison of Vital Capacity Readings and Roentgen-Ray Findings in Pulmonary Tuberculosis, Tr. National Tuberculosis Association, New York, June, 1921; Am. Rev. Tuberc. **5,** 1922. V. A Comparison of Vital Capacity Readings and Physical Signs in Pulmonary Tuberculosis, Minnesota Med. **5**: 233 (April) 1922. VI. The Significance of the Vital Capacity Test in Pulmonary Tuberculosis, Bronchial Asthma, Pneumonia and an Acute Infection Outside the Respiratory Tract, Arch. Int. Med. **30**:648-667 (Nov.) 1922.

3. Garvin, A.: Lundsgaard, C., and Van Slyke, D.: Studies of Lung Volume. II. Tuberculous Men, J. Exper. Med. **27**:87 (Jan.) 1918. III. Tuberculous Women, J. Exper. Med. **27**:129 (Jan.) 1918.

4. Ulrich, H. L., and Nathanson, M. H.: The Vital Capacity of the Lungs in Cardiac Disease, Minnesota Med. **4**:721 (Dec.) 1921.

5. Wittich, F. W.; Myers, J. A., and Jennings, F. L.: A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, J. A. M. A. **75**:1249 (Nov. 6) 1920.

6. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

7. Dreyer, G., and Burrell, L. S. T.: Vital Capacity Constants Applied to Pulmonary Tuberculosis, Lancet **2**:374 (Aug.) 1922.

factory standards for normal persons, for without these, obviously, variations from the normal cannot be accurately determined.

That the vital capacity varies according to the age, sex, height, weight, circumference of the chest, sitting height and habits of life of the normal person has been well established. Normal standards, based on a comparison of the vital capacity with these several factors, have been produced.

Hutchinson [1] concluded that the most reliable standard for estimating the vital capacity was the standing height. For every inch in increase of height between 5 and 6 feet, he estimated an increase in the vital capacity of 8 cubic inches of air. Hutchinson also noted the relation of the vital capacity to the body weight, but concluded that the variations in a normal standard were greater in comparing it to the weight than to the standing height.

Peabody and Wentworth [6] also used the height of the person for their comparisons. They placed their normal persons in three groups, and the average vital capacity for each group was calculated.

A year later (1917) Lundsgaard and Van Slyke [8] concluded that there was a more constant relationship between the vital capacity and the chest volume, calculated by measurements of the height, depth and breadth of the chest, than with any of the other standards which had previously been used.

Dreyer,[9] in 1919, compared the vital capacity with the body weight, surface area, the stem height and the chest circumference.

The data presented in this paper were calculated from tables prepared by Myers [10] from the mathematical formulas of Dreyer,[9] the graphic chart of Du Bois and Du Bois,[11] and the observations of West [12] and Myers.[13]

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8. Lundsgaard, C., and Van Slyke, D. D.: Studies of Lung Volume. I. Relation Between Thorax Size and Lung Volume in Normal Adults, Jour. Exper. Med. **27**:65 (Jan.) 1918.

9. Dreyer, G.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

10. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease. VIII. A Method for Quickly Obtaining the Percentage of an Individual's Theoretical Normal Vital Capacity of the Lungs, Am. Rev. Tuberc. **7**, No. 3 (May) 1923.

11. Du Bois, D., and Du Bois, E. F.: Clinical Calorimetry. Tenth Paper. A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. **17**:863 (June) 1916.

12. West, H. F.: Clinical Studies on Respiration: VI. A Comparison of the Various Studies for the Normal Capacity of the Lungs, Arch. Int. Med. **25**: 306 (March) 1920.

13. Myers, J. A.: Studies on Respiratory Organs in Health and Disease. II. A Study of the Vital Capacity and Physical Fitness of Nurses with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual's Physical Fitness Journal-Lancet **41**:252 (May) 1921.

The observations reported in this paper were made on a group of 738 college women at the University of Minnesota varying in age from 16 to 44 years. The measurements, with the exception of the vital capacity determinations which were made at the Students' Health Service, were taken at the Women's Gymnasium by the department of physical education at the time of a routine physical examination.

The standing height without shoes was recorded in inches, the weight without clothes in pounds and the stem height in inches.

The vital capacity in cubic centimeters was determined by means of a Sanborn water spirometer made according to the specifications of Peabody and Wentworth. A minimum of three trials was allowed and the highest reading recorded.

As the normal standards for women are based on observations on a comparatively small number of women, I felt that a comparison of a larger group of apparently normal women with the standards now accepted would be of value.

TABLE 1.—*Percentage of Vital Capacity Calculated from Body Weight*

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	283	48.34
90 to 99	215	29.11
80 to 89	142	19.24
70 to 79	84	11.38
60 to 69	9	1.21
50 to 59	5	0.67
Total	738	99.95

The percentage of vital capacity calculated from the body weight formula of Dreyer, the standing height, the surface area and the stem height was recorded for each woman. A total of 738 women were studied, although not all of the measurements were recorded on each of them.

In Table 1, the percentage of vital capacity calculated from the body weight by Dreyer's [9] formula $\frac{W^{0.72}}{V.C.} = K$ is recorded. The cases are grouped so as to compare the number and percentage of cases with the calculated vital capacity. Of a total of 738 cases, 498, or 77.45 per cent., were 90 per cent. or more of the normal standard; and 240, or 22.55 per cent., were less than 90 per cent. of the normal standard.

Data are presented in Table 2 showing the percentage of normal vital capacity calculated from the surface area. The surface area was calculated from the height and weight according to the method of Du Bois and Du Bois [11] by means of tables prepared by Myers.[10]

Of a total of 480 cases, 311, or 64.4 per cent., were above 90 per cent. of the normal standard; and 169, or 35.2 per cent., were less than 90 per cent. of the normal.

West's [12] observations on eighty-five men and forty-four women, calculating the percentage of vital capacity from the surface area, showed only 5.5 per cent. of the group less than 90 per cent. of the normal. West's group contained both men and women, and there were a comparatively large number of men with athletic training, so that a comparison of the percentage of cases less than 90 per cent. cannot be accurately made.

Table 3 shows a group of 593 cases with the vital capacity calculated according to the standing height by means of a table prepared by

TABLE 2.—*Percentage of Vital Capacity Calculated from Surface Area*

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	155	32.2+
90 to 99	156	32.2+
80 to 89	109	22.7+
70 to 79	47	9.7+
60 to 69	11	2.2+
50 to 59	2	0.4+
Total	480	99.4+

TABLE 3.—*Percentage of Vital Capacity Calculated from Standing Height*

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	114	19.2+
90 to 99	130	21.9+
80 to 89	175	29.5+
70 to 79	127	21.4+
60 to 69	41	6.9+
50 to 59	6	1.0+
Total	593	99.9+

TABLE 4.—*Percentage of Vital Capacity Calculated from Stem Height*

Percentage of Vital Capacity	Number of Cases	Percentage of Cases
100 and over	59	11.9+
90 to 99	108	21.8+
80 to 89	141	28.6+
70 to 79	129	26.1+
60 to 69	45	9.1+
50 to 59	11	2.2+
Total	493	99.7+

Myers [10] on the basis of the accepted standing height formulas. By this method, we find only 234 cases, or 41.1 per cent., that are 90 per cent. or more of the normal standard; and 349 cases, or 59.8 per cent., less than 90 per cent. of the normal.

Peabody and Wentworth,[6] in their studies of forty-four normal women, comparing the vital capacity with the standing height, found five cases, or 11.3 per cent., who were less than 90 per cent. of the normal.

In Table 4, 493 cases from the same group of college women are classified according to their normal vital capacity calculated from stem

height measurements. The stem height was supposedly measured according to the method described by Dreyer. As I shall mention later in the paper, the possibilities of error in taking stem height measurements are great.

In the 493 cases in this group, 167, or 33.7 per cent., were 90 per cent. or more than the normal standard; and 326, or 66.3 per cent., were less than 90 per cent. of the normal standard.

The two outstanding things shown in this comparison are: first, the close relation between the percentage of vital capacity calculated from the body weight formula of Dreyer and from the surface area and the fact that with both methods over 65 per cent. of the cases are more than 90 per cent. of the normal standards; second, that, confirming the

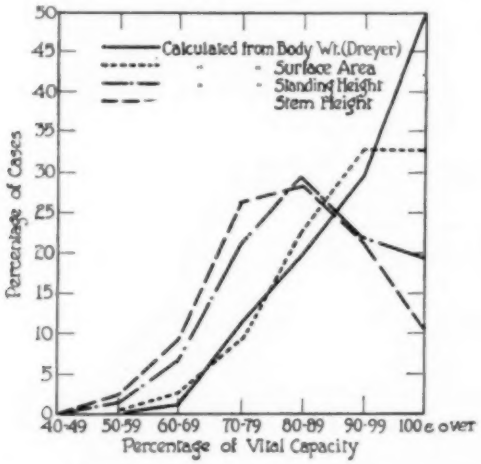

Chart 1.—The relation between the various methods of computing the normal vital capacity.

observations of Rogers [14] on a group of college men, the correlation between the stem height and vital capacity is no better than between the standing height and vital capacity. Also that apparently the normal standards for women for these two methods of computing the percentage of vital capacity are too high, since in both methods not more than 41 per cent. of the cases are above 90 per cent. of the normal.

Tables 5, 6, 7 and 8 group the persons examined according to age giving the number of cases in each age group and the average percentage of vital capacity in each age group, the vital capacity being calculated from the body weight formula of Dreyer, surface area, standing height and stem height.

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14. Rogers, W. L.: The Correlation of Vital Capacity with Stem Height. Arch. Int. Med. **31**:342 (March) 1923.

TABLE 5.—*Average Percentage of Vital Capacity Calculated from Body Weight; Grouped According to Age in Years*

Age	Number of Cases	Average Percentage Weight
16	33	91
17	136	97.41
18	198	95.17
19	119	95.58
20	63	98.12
21	30	97.33
22	24	93.16
23	14	95.92
24	8	102.87
25	4	116
26	7	92.71
27	4	95
28	3	89.66
29	3	94.66
30 and over	12	94.49
Total	658	

TABLE 6.—*Average Percentage of Vital Capacity Calculated from Surface Area; Grouped According to Age in Years*

Age	Number of Cases	Average Percentage Surface Area
16	23	85.5
17	130	94.3
18	158	93.6
19	117	92.7
20	60	93.4
21	27	93.1
22	17	89.8
23	11	91.7
24	10	92
25	3	95
26	7	84
27	3	86
28	3	86.3
29	3	89
30 and over	12	87
Total	584	

TABLE 7.—*Average Percentage of Vital Capacity Calculated from Standing Height; Grouped According to Age in Years*

Age	Number of Cases	Average Percentage Standing Height
16	25	81
17	127	89.7
18	164	89.3
19	117	87.05
20	61	87.86
21	27	86.07
22	17	85.35
23	12	90.42
24	9	90.66
25	3	83.33
26	7	77.14
27	4	84.75
28	3	78
29	3	82.66
30 and over	12	84.25
Total	591	

As we should expect with a group of persons at these ages, the curve of vital capacity percentages varies little between 16 and 30 years. The apparent decrease after 24 years of age is undoubtedly due to the small number of cases in those groups.

Chart 2 shows again the close relationship between the vital capacity calculated from the body weight formula of Dreyer and the surface

TABLE 8.—*Average Percentage of Vital Capacity Calculated from Stem Height; Grouped According to Age in Years*

Age	Number of Cases	Average Percentage Stem Height
16	25	75.2
17	139	85.4
18	177	82.5
19	123	82.1
20	65	82.6
21	29	81.8
22	20	78.4
23	13	80.5
24	11	77.5
25	4	77.2
26	8	70.3
27	6	83.3
28	3	73.3
29	4	78
30 and over	15	77.1
Total	942	

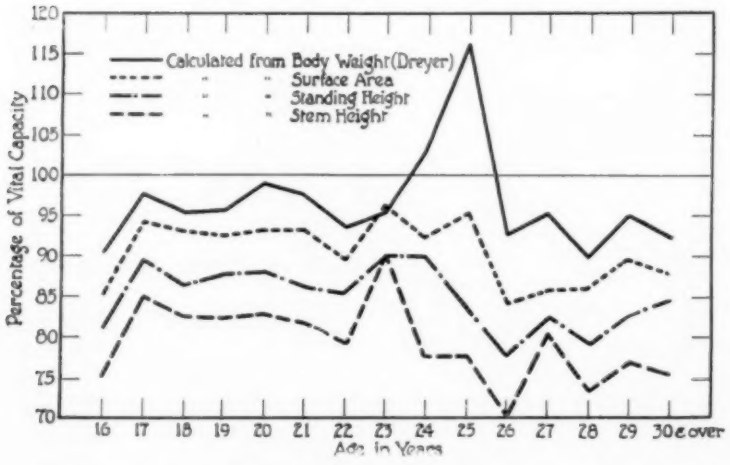

Chart 2.—Percentage of vital capacity according to age. Graphic representation of data contained in Tables 5, 6, 7 and 8.

area. With the exception of the sudden rise at age of 25 in the percentage by body weight, at no point do they differ by more than 7 per cent., the average variation being about 3 per cent. West [12] records a variation of 2 per cent. in his cases.

We again see the standing height and stem height determinations running practically parallel but at a lower level than the other two. At the age of 23 years, the average vital capacity is 90 per cent., which is the highest recorded when computed from these measurements.

In assuming that the normal standard should be 100 per cent. and a variation of 10 per cent. on either side is to be considered within the limits of normal, from observations in this group of apparently normal persons, the present standards for women would seem to be too high, especially those for calculations from the standing height and stem height. It would seem desirable that a careful study and preparation of new normal standards be made after taking measurements on a larger group of women.

That the possibility of error in taking measurements of the stem height is greater than in the others recorded is obvious. As has been

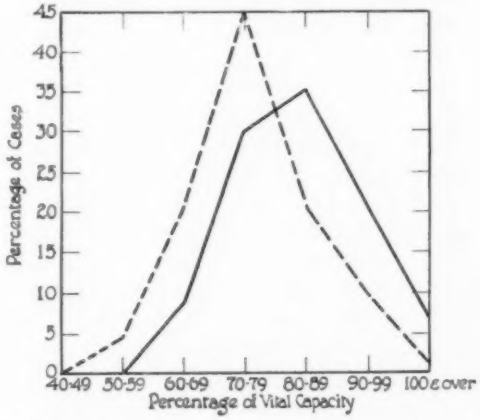

Chart 3.—This shows the great variation in the percentage of vital capacity calculated from two records of stem height on the same persons. The broken line indicates the curve calculated from measurements taken at the time of a routine physical examination; the continuous line is the curve calculated from measurements taken on the same persons at a special examination to recheck the vital capacity.

pointed out by others, the gluteal muscles may cause a variation of from 1 to 3 cm. We obtained data on a group of approximately 100 women, which illustrates clearly this possibility of error in recording the stem height. The stem height was measured at the time of a routine physical examination required for entrance to the University of Minnesota. The measurements were then taken by the department of physical education, supposedly according to the direction of Dreyer,[9] but by persons not interested especially in the use of the measurements for calculating the percentage of vital capacity.

One hundred of these same women, a few weeks later, were examined at the Students' Health Service especially for a rechecking of the measurements and records for computing their vital capacity. The stem height measurements were taken by either a nurse or a physician who were vitally interested in procuring accurate data for statistical purposes.

Because of this possible source of error in taking the stem height and the comparative small source of error in recording the body weight and surface area, for practical clinical work in vital capacity determinations it would seem advisable to advocate simply the use of weight and body surface determinations to compute the percentage of normal of a person's vital capacity. For the scientist, the stem height measurements are of value and will, of course, continue to be used. In certain cases, especially when there is a disproportion between the standing height and length of the trunk, or in obese persons, the stem height measurements give a more accurate percentage of the person's normal vital capacity.

SUMMARY

1. From observations on a group of 738 college women, varying in age from 16 to 44 years, the normal standards for the percentage of vital capacity calculated from the body weight formula of Dreyer, surface area, standing height and stem height are apparently too high, especially for the standing height and stem height.

2. The correlation of the vital capacity with the body weight as calculated by Dreyer and with the surface area are approximately equal and the most reliable for ordinary use.

3. The correlation of the vital capacity with the stem height is no better than with the standing height among college women.

4. The possibility of error in measuring stem height is so great and in measuring body weight and height so small that for practical purposes the stem height measurements may be eliminated.

THE OCCURRENCE AND SIGNIFICANCE OF THE "MYELOBLAST" UNDER NORMAL AND PATHOLOGIC CONDITIONS

PRELIMINARY ACCOUNT *

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MINNEAPOLIS

The following paper is a brief account of the results of several years of investigation of the subject indicated in the title. The complete paper with detailed discussion of the literature will be published in some European journal, because the numerous colored plates will have to be lithographed.

Naegeli [1] (1900) was the first one to express the view that the nongranular cells of the marrow are specific parenchymatous cells of this tissue which serve as the parent cells for the granular leukocytes. Naegeli stated emphatically that although they possessed some lymphoid characters, they differed from true lymphocytes in their morphologic and biologic characters, and that their origin was entirely separate from that of the lymphocytes.

But Naegeli was not the first one to express the theory of a polyphyletic origin of the blood cells, and he was not the first one to describe lymphoid cells in the marrow. Ehrlich [2] had previously asserted that each type of blood cells had its own specific parent cell, and that these were not related, except through the embryonic mesenchyme.

The occurrence of lymphoid cells in the marrow was known to many authors previous to the announcement of Naegeli's myeloblast theory. Freiberg [3] (1892) described lymphoid cells in the marrow of dogs. Arnold [4] (1895) called attention to the fact that lymphoid cells occur in the marrow of frog and man, and Hirschfeld,[5] in 1898, was the first

* Presidential address delivered before the Minnesota Pathological Society, May, 1923. From the Hematological Laboratory, Department of Animal Biology, University of Minnesota. Aided by a grant from the Research Funds of the Graduate School.

1. Naegeli, O.: Ueber rotes Knochenmark und Myeloblasten, Deutsch. med. Wchnschr. **26**:287, 1900. Blutkranheiten und Blutdiagnostik, Berlin u. Leipzig, Vereinigungwiss. Verleger, 1919.

2. Ehrlich, P., and Lazarus, A.: Die Anämie, Pt. 1, Normale und pathologische Histologie des Blutes, 1898.

3. Freiberg, H.: Experimentelle Untersuchungen über die Regeneration der Blutkörperchen im Knochenmark, Thesis, Dorpat, 1892. (Cited from Weidenreich.)

4. Arnold, J.: Zur Morphologie und Biologie der Zellen des Knochenmarks, Virchows Arch. f. path. Anat. **140**:411, 1895.

5. Hirschfeld, H.: Zur Kenntnis der Histogenese der granulierten Knochenmarkszellen, Virchows Arch. f. path. Anat. **153**:335, 1898. Ueber akute Leukämie, Folia Haematol. **4**:202, 1907. Die unitarische und dualistische Auffassung über die Histopathologie der Leukämien, Folia Haematol. **6**:382, 1908.

to claim that they differentiated into granular leukocytes. He stated that these cells were not necessarily lymphocytes, although he could see no morphologic difference between them and true lymphocytes of the lymphatic tissues and blood. Engel,[6] Jolly,[7] and Pappenheim[8] also described lymphoid cells in the marrow previous to the birth of Naegeli's myeloblast. Pappenheim, in 1899, stated that these lymphoid cells are identical with Troje's[9] marrow cells and also with the lymphocytes of the blood and lymphatic tissues.

Naegeli's view of the specific nature of the myeloblast was soon accepted by many, notably Schridde,[10] but not all of those who accepted the dualistic view were willing to grant the existence of specific morphologic characters for the myeloblast which would always distinguish it from the lymphocyte or lymphoblast. Michaelis and Wolff[11] (1901) describe "indifferent lymphoid cells" in the marrow which change to granular leukocytes. They believe that lymphocytes, on the other hand, are differentiated lymphoid cells without the capacity for granular differentiation. However, they could see no morphologic difference between lymphocytes and the indifferent lymphoid cells of the marrow. Türk[12] (1904) designated the undifferentiated marrow cells as "lymphoid marrow cells." The only distinction between them and lymphocytes is the fact that the marrow cells differentiate while the lymphocytes do not. There are no morphologic distinctions, but they should be kept separate nevertheless. Butterfield, Heineke and Meyer[13] although

6. Engel, C. S.: Weitere Beiträge zur Entwickelung der Blutkörperchen beim menschlichen Embryo, Arch. f. mikr. Anat. **53**:322, 1898.

7. Jolly, J.: Recherches sur la division indirecte des cellules lymphatiques granuleuses de la moelle des os, Arch. d'Anat. Microscop. **3**:168, 1899-1900.

8. Pappenheim, A.: Vergleichende Untersuchungen über die elementare Zusammensetzung des roten Knochenmarks einiger Säugetiere, Virchows Arch. f. path. Anat. **157**:19, 1899. Atlas der menschlichen Blutzellen, Jena, G. Fischer, 1905-1912. Ueber die Deutung und Bedeutung einkerniger Leukocytenformen in entzündlichen Zellanhaufungen mit besonderer Rücksicht auf die lokale Eosinophilie, Folia Haematol. **8**:1, 1909. Zur vorstehenden Mitteilung Dominici's, Folia Haematol. **8**:107, 1909. Ueber die Wandlung des Lymphoidozytenbegriffs und der Blutstammzellen, Folia Haematol., Arch. **21**:207, 1917. Morphologische Hämatologie, Leipzig, W. Klinkhardt, 1919. Pappenheim, A., and Hirschfeld, H.: Ueber akute myeloide und lymphadenoide makrolymphozytäre Leukämie an der Hand von zwei verschiedenen Fällen, Folia Haematol. **5**:347, 1908.

9. Troje: Cited from Pappenheim.

10. Schridde, H.: Myeloblasten, Lymphoblasten und lymphoblastische Plasmazellen, Ziegler's Beitr. z. path. Anat. u. z. allgem. Path. **41**:223, 1907.

11. Michaelis, L., and Wolff, A.: Die Lymphocyten, Deutsch. med. Wchnschr. **27**:651, 1901.

12. Türk, W.: Berichte aus den wissenschaftlichen Vereinen, Wiener med. Wchnschr. **54**:1430, 1904. Vorlesungen über klinische Hämatologie, Pt. 1, Wien, 1904. Ueber die Beziehungen zwischen myeloidem und lymphatischem Gewebe im Verlaufe von Leukämien, Verh. d. Kongr. f. innere Med. **23**:585, 1906.

13. Butterfield, E. E.; Heineke, A., and Meyer, E.: Ueber das Vorkommen der Altmannschen Granulationen in den weissen Blutzellen, Folia Haematol. **8**:325, 1909.

accepting the dualistic view, state that all of the morphologic characters claimed for the lymphoblast by Naegeli and Schridde are also to be found in the myeloblast, including the Altmann-Schridde granules.

Helly [14] (1910) follows the old Ehrlich view and believes that the myelocyte is the most primitive type of granular cell in the marrow. He states that granular leukocytes are derived from nongranular cells normally only in the embryo. In pathologic human and experimental mammalian marrow he finds them only in cases showing signs of anemic degeneration, and he, therefore, sees in them signs of an exhausted process of blood formation. Most of them are dedifferentiated erythroblasts, but some are dedifferentiated neutrophil myelocytes, and some are ordinary lymphocytes.

Opposed to the dualistic and polyphyletic views is the unitarian or monophyletic theory of the origin of blood cells. According to this view, all of the blood cells are related and they are all descended from one type of parent cell. The extreme unitarian view as represented by Maximow,[15] Weidenreich,[16] Danchakoff [17] and their followers, accepts the lymphocyte as this parent cell, but according to Pappenheim,[*] Ferrata [18] and their school, the parent cell is the myeloblast of Naegeli which in the normal adult is to be found in the bone marrow only. The lymphocyte is descended from this "lymphoidocyte," as Pappenheim calls it, in the embryo, while the lymphocytes of the adult are maintained by partially differentiated lymphoblasts of the lymphatic tissue and organs. Pappenheim recognizes the possibility of relations between granular leukocytes and lymphocytes by way of the dedifferentiated lymphocyte which has reverted to the lymphoidocyte stage and is then capable of differentiating into a granular leukocyte. For the normal adult Pappenheim is willing to admit that the cell which Naegeli described as a myeloblast is to be found only in the marrow; but, nevertheless, it may show relationships with the lymphocytes, for it may occur in the acute lymphatic leukemias, and lymphocytes are derived from it in the embryo.

14. Helly, K.: Kritik der sogennanten Myeloblasten, Verhandl. d. deutsch. path. Gesellsch. **14**:198, 1910. Aämische Degeneration und Erythrogonien, Ziegler's Beitr. z. path. Anat. u. allgem. Path. **49**:15, 1910.

15. Maximow, A.: Der Lymphozyt als gemeinsame Stammzelle der verschiedenen Blutelemente in der embryonalen Entwicklung und im postfetalen Leben der Säugetiere, Folia Haematol. **8**:125, 1909. Experimentelle Untersuchungen zur postfetalen Histogenese des myeloiden Gewebes, Ziegler's Beitr. z. path. Anat. u. Allgem. Path. **41**:122, 1907.

16. Weidenreich, F.: Die Leukocyten und verwandte Zellformen, Wiesbaden, J. F. Bergman, 1911.

17. Danchakoff, V.: Origin of the Blood Cells. Development of the Haematopoetic Organs and Regeneration of the Blood Cells from the Standpoint of the Monophyletic School, Anat. Rec. **10**:397, 1916.

18. Ferrata, A.: Le emopatie, Milano, Società Editrice Libraria **1**, 1918.

Maximow [15] and Weidenreich [16] do not agree with this view; they deny the existence of the myeloblast and lymphoidocyte and claim that there is abundant evidence for the differentiation of granular leukocytes and erythrocytes from the true lymphocyte. The so-called myeloblast is merely a temporary variation form of the lymphocyte, which is of no significance; or the structure which has been described for it is the result of the dry smear method on which most of the descriptions of this cell are based. With the section method they can see no difference between lymphocytes and the nongranular cells of the marrow.

Maximow admits that in newly born animals there are certain differences between myeloblasts and lymphoblasts, but these differences are slight, and the differences between the myeloblasts are often greater than those between myeloblasts and lymphoblasts, and they are not sufficient to justify sharp division between the two. They may be accounted for by the different mediums in which the cells are located.

No one who has worked with the blood from a case of myelogenous leukemia will agree with Maximow's and Weidenreich's denial of the existence of the cell described by Naegeli as the "myeloblast." On the other hand, there has accumulated a large body of evidence in favor of their view of the possible derivation of granular leukocytes from true lymphocytes. The following may be cited as examples of this type of evidence:

Delamare [19] (1901) found esosinophil myelocytes in the follicles of normal lymph nodes of rabbits and pigs. The nuclei of these myelocytes resembled those of lymphocytes both in size and distribution of chromatin. All intermediate stages between lymphocytes and polymorphonuclear eosinophils were found, and some of the cells contained only a few granules. He also found nucleated reds within the follicles of a mesenteric lymph node of a gray rat.

Stschastny [20] (1905) obtained general and local eosinophilia by injections of foreign erythrocytes and hemolytic serums. Mononuclear eosinophils were found in the peritoneal exudate, in the lungs, lymph nodes and spleen. Their nuclei resembled those of large mononuclears and lymphocytes. Typical myelocytes were not found.

Dominici [21] obtained the differentiation of myelocytes within the follicles and germ centers of lymph nodes and spleen of rabbits with

19. Delamare, G.: Note sur les cellules éosinophiles et les hématies nuclées du ganglion lymphatique normal, C. R. de la Soc. de Biologie **53**:849, 1901.

20. Stschastny, S. M.: Ueber die Histogenese der eosinophilen Granulationen im Zusammenhang mit der Hämolyse, Ziegler's Beitr. z. path. Anat. u. z. allgem. Path. **38**:456, 1905.

21. Dominici, H.: De l'origine lymphatique ou amyéloide des polynucléaires ou leucocytes granuleux à noyau polymorphe, Folia Haematol. **8**:97, 1909. Etudes sur le tissu conjonctif et les organes hématopoiétiques des mammifères, Arch. d'Anat. Microscop. **17**:1, 1921.

experimental infections and repeated bleedings. He also noted myeloid metaplasia of the lymphocytes of the taches laiteuses of the omentum of rabbits infected with taeniae, and this observation was confirmed by Pappenheim.

Maximow [15] ligated the vessels of the kidney, an operation which resulted in the production of bone and bone marrow within the kidney. The myeloid cells of the marrow could be traced to the lymphocytes which migrated from the vessels. Some of these lymphocytes began their differentiation to granular leukocytes while they were still in the vessels. Recently Maximow has obtained the differentiation of lymphocytes from cultures of lymph nodes grown with cell-free bone marrow extract.

Weidenreich and I [22] described and figured the differentiation of small and medium sized lymphocytes to granular leukocytes in the lymph nodes of the weasel. The small myelocytes were of special significance, for they were of the size of small lymphocytes, and their nuclei had exactly the same structure and the same amount of chromatin as the nuclei of the surrounding small lymphocytes. Typical myelocytes with pale nuclei were also noted in the same preparation. This checks with Dominici's observation that lymphocytes can differentiate into granulocytes without change in their inner nuclear characters, or the nuclei may change to the myelocyte type, giving two types of mononuclear granulocytes. The myelocytic type is the common one for the marrow, while the lymphocytic type is more frequent in the tissues.

According to Weidenreich and Weill [23] myelocytes are common in the hemolymph nodes of sheep and other animals and in the normal mucosa of the digestive tract and in the thymus of adult man. They derive these cells from lymphocytes.

I have obtained myeloid metaplasia of lymphocytes of all types in the omentum of rabbit surrounding a graft of foreign tissue, and I have also confirmed Dominici's observation of the occurrence of myelocytes within the follicles of lymph nodes of rabbits which have been bled repeatedly.

Recently one of my students, Dr. Logefeil, observed extremely small myelocytes, no larger than a small lymphocyte, with small dark

22. Downey, H., and Weidenreich, F.: Ueber die Bildung der Lymphozyten in Lymphdrüsen und Milz, Arch. f. mikr. Anat. **80**:306, 1912.

23. Weill, P.: Ueber die Bildung von Leukozyten in der menschlichen und tierischen Thymus des erwachsenen Organismus, Arch. f. mikr. Anat. **83**:305, 1913. Ueber die Bildung von granulierten Leukozyten im Karzinomgewebe, Virchows Arch. f. path. Anat. **226,** No. 2, 1919. Ueber die leucocytären Elemente der Darmschleimhaut der Säugetiere, Arch. f. mikr. Anat. **93**:1, 1919. Ueber das regelmässige Vorkommen von Myelocyten in der Milz des erwachsenen Menschen, Arch. f. mikr. Anat. **93**:82, 1919.

nuclei absolutely identical with those of the surrounding small lymphocytes in a case of mixed leukemia.

These facts, and many more which might be cited, prove beyond question that lymphocytes may under certain conditions differentiate into myeloid cells, that is, granular leukocytes and red cells. Normally, this may occur to a limited extent in the thymus and intestine, but not in lymph nodes or human spleen.

However, these facts do not dispose of the myeloblast as readily as many of those who hold the unitarian view seem to think, for, as every pathologist knows, a cell of that structure does exist, at least in the leukemic blood. But it does not necessarily follow that the cell is a myeloblast in Naegeli's sense; that is, it does not have to be a cell which occurs in the normal marrow and only in the marrow. It may be an atypical pathologic cell type which does not occur in the normal person, or it may be a dedifferentiated myelocyte or erythrocyte, as claimed by Helly. Naegeli believes that the cell is specific for the marrow and that it is in no way related to the lymphocyte. I shall discuss his statements one at a time.

NAEGELI'S THEORIES

Morphologic.—Naegeli's morphologic criteria for distinguishing the myeloblast have undergone considerable change since 1900, the distribution of the nuclear chromatin in the form of a delicate network being the only one of the original Naegeli characters to stand the test of time. Absence of nucleoli in the myeloblast was at first one of its distinguishing features, but now Naegeli claims that the myeloblast has from two to four nucleoli and the lymphoblast one to two. Butterfield,[24] Schridde[10] and others have shown that the number of nucleoli is inconstant for the individual cells of the the two types. It still remains a fact, however, that on the average the myeloblasts have smaller, more rounded and more numerous nucleoli, while the nucleoli of lymphocytes are usually not so numerous, are larger and more irregular in outline and more deeply stained.

Naegeli states that the granules which may occur in myeloblasts are unripe neutrophil granules and not azure granules, as is claimed by other workers. Few agree with Naegeli on this, but many recognize a special type of myeloid azure granulation which may occur in myeloblasts and leukoblasts, but not in lymphocytes.

Naegeli made much of the Schridde fuchsinophil granules which were supposed to be specific for lymphoblasts until Butterfield, Meyer

24. Butterfield, E. E.: Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz-, Leber- und Lymphdrüsen, Deutsch. Arch. f. klin. Med. **92**:336, 1908.

and Heineke [24] and Wallgren [25] showed that they can occur in myeloblasts also. They have been shown to be mitochondria which may occur in all blood and tissue cells and are, therefore, not specific for any one type of cell. According to Naegeli's latest view, these granules occur in lymphoblasts and myeloblasts of smears, but not in the myeloblasts of sections. Those in the myeloblasts are in the form of short threads or commas, while those of the lymphoblasts are short rods located in the perinuclear area.

Biologic Differences.—Proteolytic and oxydase ferments occur in myeloblasts but not in lymphoblasts. Sometimes the oxydase is absent from myeloblasts, but this is due to injury of the cell.

I have not investigated the oxydase reaction, but a few statements from the literature are of interest.

M. L. Menten [26] concludes that the reaction is an adsorption phenomenon dependent on properties of intracellular surfaces. It is not specific for myeloid cells, for lymphocytes give a well marked reaction, although the reaction is stronger in eosinophil and neutrophil leukocytes. Many tissues give the reaction, so it is by no means specific for blood cells.

Hynek [27] refers to a case of myelogenous myeloblastic leukemia in which the myeloblasts did not give the reaction, and he also refers to a case of Decastello in which the reaction was negative.

Klein [28] showed that lymphocytes also give the reaction, and W. Schulze [29] found that the myeloblasts of the normal marrow usually do not give the reaction, while the pathologic myeloblasts in blood and organs in myeloblastic leukemia are usually positive.

Citron [30] states that negative oxydase reaction is frequently found in undoubted myeloid-leukemic changes, and so it does not determine the myeloic or lymphatic nature of the condition. Positive reaction proves myeloid cell nature existing at the time, but does not tell us anything of the genesis of these myeloid cells, as from previously negatively reacting lymphocytes.

Histologic Differences.—Myeloblasts are found normally only in the marrow, never in lymphatic organs, especially not in follicles or germ

25. Wallgren, A.: Zur Kenntnis der lymphoiden Zellen des Kaninchenblutes, Folia Haematol. **8**:307, 1909.

26. Menten, M. L.: A Study of the Oxydase Reaction with Alpha-Naphthol and Para-Phenylenediamine, J. M. Res. **40**:433, 1919.

27. Hynek, K.: Zur Monozytenfrage, Folia Haematol., Arch. **13**:345, 1912.

28. Klein, S., cited from E. Neumann: Virchows Arch. f. path. Anat. **207**: 379, 1912.

29. Schulze, W.: Zur Differentialdiagnose der Leukämieen, München. med. Wchnschr. **56**:167, 1909.

30. Citron, J.: Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie Folia Haematol., Arch. **20**:1, 1915.

centers. Under no circumstances are myelocytes ever developed in the follicles and germ centers of lymph nodes and spleen. When myeloid metaplasia occurs it is always in the pulp or interfollicular and medullary tissue of lymph nodes. The myeloid and lymphatic tissues are antagonistic to one another; if one hypertrophies, the other is suppressed or crowded out. In myelogenous leukemia the follicles are reduced or entirely suppressed, while in lymphatic leukemia there is a great overgrowth of follicles at the expense of the pulp and medullary tissue.

These are complex questions, and their complete discussion would require many pages. However, a few statements from the literature with some observations of my own and of my students will prove that there is something to be said on the other side of these questions.

First, in regard to the statement that myeloblasts and myelocytes can never occur in the follicles: Dr. H. Z. Giffin [31] has reported a case of persistent eosinophilia in which I have found eosinophil myelocytes in the germ centers of the follicles of the spleen, and myelocytes were observed by Dominici and myself in the follicles of lymph nodes of rabbits which had been bled repeatedly. Roman [32] observed myelocytes in the germ centers of tonsillar follicles and also in the germ centers of the follicles of a cervical lymph node in a case of myelogenous chloroleukemia. This is not interpreted as an invasion of the germ centers from the outside, because there were few myelocytes in the immediate vicinity of the follicles. In spite of the fact that the author is a dualist, he interprets his findings as indicating true myeloid metaplasia of the germ centers.

That myeloblasts may also occur in the follicles was shown by Citron [30] and by one of my students, Dr. Fineman.[33] Both of these cases were cases of lymphatic leukemia in which most of the lymphoid cells of the blood were of the myeloblastic type. In Citron's case the marrow was normal and the myeloblasts were seen to be coming from the follicles and germ centers as well as from other parts of the nodes. Fineman was unable to get marrow from his case, because necropsy was not permitted, but a lymph node removed at biopsy during the height of the proliferative activity showed the myeloblastic type of cell all through the node. Clinical observation of the case permits the assumption that all of the cells of myeloblastic type which were noted in the blood were coming from the lymph nodes rather than from the marrow, for there was no evidence of increased marrow activity.

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31. Giffin, H. Z.: Persistent Eosinophilia with Hyperleucocytosis and Splenomegaly, Am. J. M. Sc. **158**:618, 1919.

32. Roman, B.: Zur Kenntnis der myeloischen Chloroleukämie, Ziegler's Beitr. z. path. Anat. u. z. allgem. Path. **55**:61, 1913.

33. Fineman, S.: A Study of Microlymphoidocytic Leukemia, Arch. Int. Med. **29**:168 (Feb.) 1922.

The supposed antagonism between the lymphatic and myeloid tissues is the strongest point urged by the dualists in favor of their view of the specific myeloid nature of the myeloblast. At first thought this argument seems difficult to meet, but this is true only when one fails to consider all of the known facts in the case. The literature contains many observations against this view, and I and my students can add more.

Werzberg [34] and Hertz,[35] studying experimental myeloid metaplasia, showed that myeloid metaplasia may occur at a time when there is hypertrophy of the follicles. Sternberg [36] states that in myelogenous leukemia the relative abundance of pulp and follicles of the spleen is extremely variable. In some cases both pulp and follicles are equally enlarged, and in others the hypertrophy involves either the follicles or the pulp. The pulp may be greatly increased and the follicles only slightly so, or the follicles may be completely suppressed. Myelocytes may occur in the follicles. Follicles of lymph nodes may also contain myelocytes, especially in their peripheral parts.

Isaac and Cobliner [37] report two cases in which the blood was that of chronic lymphatic leukemia, while the histologic changes of the organs were those commonly found in myelogenous leukemia. Pappenheim states that myelogenous leukemia may occur with a normal marrow, and lymphatic leukemia may be centered in the marrow leaving the lymph nodes normal.

Hirschfeld [5] cites a number of cases of acute leukemia which show all of the intermediate stages between acute lymphatic and acute myelogenous leukemia. He concludes that this is proof for the correctness of the unitarian view, and that this view gives the only explanation for these variations in the character of the cases cited.

Cases of so-called mixed leukemia, that is, cases in which the lymphatic and myeloid tissues show equal activity, are of special importance in deciding this question. Such cases have been reported by Decastello,[38] Türk,[12] Hirschfeld,[5] Herxheimer [39] and A. Herz.[40] In

34. Werzberg, A.: Neue experimentelle Beiträge zur Frage der myeloiden Metaplasie, Virchows Arch. f. path. Anat. **204**:272, 1911.

35. Hertz, R.: Zur Frage der experimentellen myeloischen Milz-Metaplasie, Zeitschr. f. Klin. Med. **71**:435, 1910.

36. Sternberg, C.: Primärerkrankungen des lymphatischen und hämatopoetischen Apparates; normale und pathologische Morphologie des Blutes, Ergeb. d. allgem. Path. u. path. Anat. (Lubarsch-Ostertag) **9**:360, 1905.

37. Isaac, S., and Cobliner, S.: Ueber mikrolymphozytäre Typen akuter myeloischer Leukämieen, Folia Haematol., Arch. **10**:459, 1910.

38. Von Decastello, A.: Ueber Leukopenie und kleinlymphozytäre Umwandlung des Knochenmarkes bei chronischer myeloischer Leukämie und bei Sepsis, Folia Haematol., Arch. **13**:471, 1912.

39. Herxheimer, G.: Ueber einen kombinierten Fall von lymphatischer und Myeloblastenleukämie, Zentralbl. f. allgem. Path. **24**:897, 1913.

40. Herz, A.: Zur Frage der gemischten Leukämie, Wiener klin. Wchnschr. **22**:1030, 1909. Die akute Leukämie, Leipzig, F. Deuticke, 1911.

spite of the pronounced activity of both systems, these authors, except Hirschfeld, thought that the two remained distinct and separate. One of our own cases, however, which has just been worked over by Dr. Logefeil, shows free mixing of the cells of the two systems. The liver shows the changes characteristic of lymphatic leukemia. Portions of the spleen show extensive myeloid metaplasia, but in other parts there is a decided overgrowth of lymphatic tissue. In the lymph nodes there is diffuse lymphatic increase accompanied by myeloid metaplasia. The leukemic infiltration of the lungs, kidneys and pancreas consists of lymphocytes and myelocytes freely mixed. The blood of this case is also mixed, and it is evident that both myelocytes and lymphocytes are derived from the myeloblast. The diagnosis of mixed leukemia was first made from the blood and the organ changes were found to be just as anticipated from the blood findings.

These reports from the literature and our own findings are surely not in line with the usual dualistic conception of the antagonism of the one tissue for the other. One of the strongest arguments of the dualists, therefore, falls to pieces.

RESULTS OF AUTHOR'S RESEARCHES

But the myeloblast of Naegeli as a cell type still remains. I have already presented some evidence to indicate that this cell is not a specific bone marrow cell. My personal investigation of this question extending over several years has uncovered more facts in favor of this view. It is this work which I now wish to consider briefly.

The question is too complex to be solved by the use of any one method or of any one type of material. The conflicting views on this subject are undoubtedly due largely to the fact that past work has been too one-sided. The anatomists have relied on the section method and have failed to study the pathologic material. Pathologists and clinicians, on the other hand, have pinned their faith to the pathologic material, largely human, and seem to have forgotten that normal tissues and organs are still to be had. Some are also unaware of the fact that anatomists and histologists have worked on blood and have even written about it.

In my own work I have tried to avoid the foregoing objections by utilizing a great variety of normal, pathologic and experimental material and by considering all of the available literature.

It seems almost axiomatic that in a problem of this kind one should turn first to the normal tissues, but curiously this side of the problem is the one which has received the least attention in the past.

In the course of the work it soon became evident that the section method is the least reliable. By this method the finer nuclear structures which we are accustomed to see in the blood smears disappear, and it

is indeed difficult if not impossible to distinguish between the lymphocytes of lymph nodes and the lymphoid cells of the marrow. Fine smears of marrow and lymph nodes can be obtained if they are fixed in Helly's fluid while they are still moist and then treated as though they were sections. But even with this method it is impossible to distinguish the finer details, and therefore impossible in many cases to compare tissue cells with cells of the blood smears as usually prepared. After much work with this method it was finally abandoned in favor of the dry smear method as practiced for blood smears with Wright's stain. It was impossible to overcome the difficulty of making satisfactory dry smears of marrow and lymph nodes, but by making them in large numbers and selecting only the best slides abundant good material was obtained.

The results of the work on normal human and mammalian organs can be summarized briefly.

(1) Myeloblasts exist in the normal marrow of human and mammalian adults. They occur in small numbers, because blood regeneration is largely homoplastic. They are far more numerous in the young and new-born in whom heteroplastic regeneration is more pronounced. They do not occur in lymph nodes and spleen nor in the normal blood. The peculiar myeloid type of azure granulation described by Pappenheim and others and frequently noted in the myeloblasts of the leukemic blood was found in the myeloblasts of human marrow, but not in those of rabbits.

(2) Myeloblasts occur in the blood and lymph nodes in small numbers in newly born rabbits. The human new-born has not yet been investigated with reference to this particular question.

(3) We have several cases of acute lymphatic leukemia with myeloblasts in the blood and tissues. In these cases all intermediate stages lead from the myeloblast to fully matured lymphocytes, so there can be no doubt that there are relations between them.

(4) We also have two cases of mixed leukemia in which both lymphocytes and myeloid cells are derived from the myeloblasts of the blood. Organ changes which have already been described correspond to the blood findings.

CONCLUSIONS

These observations justify the following conclusions:

(1) Incomplete morphologic dualism exists in the normal mammalian and human adult. The myeloblast is a real stem cell of the myeloid cells of the marrow. Lymphocytes of lymph nodes and spleen are regenerated by mitosis of their own kind and by derivation from the reticulum without the intervention of the myeloblast. The lymphocyte has not lost its capacity for further differentiation, as is evidenced

by the fact that normally some of those located in the intestinal mucosa, thymus and hemolymph nodes may differentiate into granular leukocytes. The differentiation of tissue mast cells and plasma cells from lymphocytes is also a well-known process.

(2) Under pathologic and experimental conditions which cause myeloid metaplasia the derivation of myeloid cells from lymphocytes without the intervention of the myeoblast may be an extensive process.

(3) In the myelogenous and acute lymphatic leukemias the myeloblast may serve as the stem cell of both lymphocytes and myeloid cells, and this may take place in the same person in cases of mixed leukemia. For the myeloid series this can be accounted for by the differentiation of cell types which normally exist in the marrow, but for the lymphocytes the relation with the myeloblast must be explained by factors which do not exist in the normal person. Dedifferentiation of the lymphocytes to the myeloblast, which is the equivalent of the primitive blood cell of the embryo, at least so far as one can judge from sections, may be one factor. Excessive liberation of free cells from the reticulum with retardation or complete failure of differentiation may be another factor. Evidence for this was obtained from Dr. Fineman's[33] case of lymphatic leukemia, in which many of the myeloblasts of the node could be traced to the fixed tissue. Under normal conditions the nuclei of such cells change rapidly, even before the cells have become free, but in this case they remained practically identical with those of the fixed cells of the reticulum. Such nuclei are of the myeloblastic type. These myeloblasts show all transitions to lymphocytes, as was proved by Fineman,[33] and true lymphocytes undoubtedly result from their differentiation. This may also be true of the few lymphocytes which occur normally in the bone marrow, although no one has succeeded in working this out for the normal marrow.

The position of the myeloblast may now be defined with some accuracy. It probably corresponds to the primitive blood cell of the embryo and is retained in the normal adult only in the marrow, where it is primarily related to the cells of the myeloid series. In newly born rabbits it also occurs in limited numbers in the blood and lymphatic tissues. In the leukemias it may revert to its primitive relations with the fixed tissue on the one hand and the lymphocytes and myeloid cells on the other.

The lymphocyte is to be regarded as a specialized or partly differentiated cell endowed with myeloid potentialities which usually do not develop, but which may do so when the proper stimulus is applied; in other words, their function and structure is not a fixed entity as is the case with the mature myeloid cells.

It is interesting to note that Naegeli,[1] who is the chief defender of the dualistic view, is at heart a unitarian. The following statement

occurs in the third edition of his handbook: "When myeloid cells occur in lymphatic tissue they are always of perivascular origin from indifferent mesenchyme cells. The same is true of lymphocytes when they occur in myeloid tissue. The blood vessels are surrounded by indifferent mesenchyme cells which in the adult may differentiate in either direction."

THE VALUE OF CAFFEIN AS AN ANTIDOTE FOR MORPHIN *

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A study of the combined action of two drugs is of both theoretical and practical interest. From the practical standpoint, the result of such a study may shed light on the value of either drug in the abnormal states encountered in disease; with more certainty, it may give information regarding the efficacy of one drug as a physiologic antidote for the other. The comparative frequency of morphin poisoning, the frequent subcutaneous administration of the poison and the fact that considerable time may elapse before the patient comes under treatment, all combine to render it desirable that we possess a satisfactory physiologic antidote against morphin. For this purpose, several drugs have been proposed; of these, caffein alone seems to have met with almost universal approbation. The present investigation was undertaken to ascertain whether this favorable view could be supported by experimental evidence.

EXPERIMENTS WITH MORPHIN AND CAFFEIN PERFORMED ON CATS

The first experiments were carried out on cats. Using a method essentially the same as that described by Hatcher and Brody [1] for the assay of digitalis, the attempt was made to ascertain the fatal dose of morphin sulphate for these animals by slow intravenous injection. The cats were lightly etherized for operation; and a cannula, connected with a buret containing a solution of morphin sulphate, 1 per cent. in physiologic sodium chlorid solution, was inserted into the femoral vein. The morphin sulphate solution was injected at the rate of 1 c.c per kilogram of body weight every two minutes until the death of the cat appeared imminent, when the rate of injection was materially reduced. Somewhat to our surprise, it was found, by the use of nine cats, that the lethal dose of morphin administered in this way did not vary widely, the average being 390 mg. of morphin sulphate per kilogram of body weight; the extremes, 310 and 440 mg. per kilogram.

Salant and Rieger [2] state that the average minimum lethal dose of caffein administered orally to cats is 150 mg. per kilogram of body

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* From the Laboratory of Pharmacology, Medical College of Virginia.

1. Hatcher, R. A., and Brody, J. G.: The Biological Standardization of Drugs, Am. J. Pharmacy **82**:360 (Aug.) 1910.

2. Salant, W., and Rieger, J. B.: The Toxicity of Caffein, Bull. 148, Bureau of Chemistry, U. S. Dept. of Agriculture.

weight. Pilcher [3] has observed death to follow a dose of 60 mg. per kilogram; but evidently he regards this as exceptional, placing the average minimum lethal dose at about 120 mg. per kilogram. Although it is possible that season or locality may influence the resistance of cats to caffein intoxication, the assumption that 80 mg. of caffein per kilogram, administered orally in the form of a 1 per cent. solution of the base, would prove fatal only in exceptional cases seemed justifiable. Consequently, this dose was given to each of a series of six cats; and in from fifteen to thirty minutes, the animals were etherized and given the morphin injections as in the preceding series in which morphin alone was used. The average amount of morphin sulphate required to cause the death of these "caffeinized" cats was less than that necessary for the untreated animals; being 303 for the former and, as previously stated,

TABLE 1.—*Lethal Dose of Morphin Alone or with Caffein Given Cats by Intravenous Injection*

Weight of Cat in Kg.	Dose of Caffein in Mg. per Kg.	Dose of Morphin in Mg. per Kg.	Average
2.0	0	310	
2.9	0	310	
2.8	0	390	
3.4	0	390	
2.3	0	410	390
2.2	0	410	
3.4	0	420	
2.1	0	430	
2.5	0	440	
3.5	80	280	
2.9	80	290	
2.5	80	310	303
3.8	80	310	
3.1	80	320	
2.4	80	360	

390 mg. per kilogram for the latter. So far as one may draw conclusions from so limited a number of experiments, a large, but not necessarily fatal, dose of caffein lowers the resistance of cats to the toxic action of morphin. The condensed protocols of these experiments are given in Table 1.

An effort was made to determine the average minimum lethal dose of morphin sulphate injected subcutaneously into cats. Sollmann, quoting Mueller,[4] states that the fatal dose of morphin for cats varies from 40 to 80 mg. per kilogram. In our experiments, four of the seven cats that received 20 mg. of morphin sulphate per kilogram alone succumbed; while the animals that were given doses of 25, 30, 35, and 40 mg. per kilogram survived.

3. Pilcher, J. D.: Alcohol and Caffein: A Study of Antagonism and Synergism, J. Pharmacol. & Exper. Therap. **3**:267 (Jan.) 1911-1912.

4. Sollmann, T.: A Laboratory Guide in Pharmacology, Philadelphia, W. B. Saunders Company, 1917.

On the other hand, of the nine cats that were given 20 mg. of morphin and from 15 to 20 mg. of caffein, seven died; and two cats died that received 30 and 35 mg. per kilogram of morphin sulphate, respectively, in conjunction with 20 mg. of caffein per kilogram. The results are summarized in Table 2.

Table 2 shows that the mortality following a dose of 20 mg. of morphin sulphate per kilogram alone is a little more than 57 per cent.; but when the animal receives 15 or 20 mg. of caffein per kilogram, the mortality is increased to a little more than 77 per cent. Moreover, the cats that were given 25, 30, 35 and 40 mg. of morphin alone survived; while doses of 30 and 35 mg. of morphin per kilogram proved fatal when combined with a dose of 20 mg. of caffein per kilogram.

TABLE 2.—*Lethal Dose of Morphin Alone or with Caffein Given by Subcutaneous Injection into Cats*

Weight of Cat in Kg.	Caffein in Mg. per Kg.	Morphin in Mg. per Kg.	Result
1.72	0	20	Survived
2.10	0	20	Survived
2.07	0	20	Survived
2.21	0	20	Died
1.70	0	20	Died
2.04	0	20	Died
2.33	0	20	Died
1.81	0	25	Survived
1.81	0	30	Survived
1.86	0	35	Survived
2.04	0	40	Survived
2.41	20	20	Survived
2.33	15	20	Died
1.59	20	20	Died
1.70	20	30	Died
1.81	20	30	Died
2.07	20	30	Died
2.00	15	30	Died
1.99	15	20	Died
2.41	15	30	Died
2.27	20	30	Died
2.30	20	35	Died

EXPERIMENTS WITH MORPHIN AND CAFFEIN PERFORMED ON GUINEA-PIGS

It is a well-known fact that morphin causes excitement in the cat and that death often occurs during convulsions. Caffein also has this effect on cats; so that it would seem quite possible that caffein might act deleteriously in morphin poisoning in cats; and, on the other hand, exert a favorable influence where this apparent synergism is absent. For this reason, guinea-pigs were selected for the next experiments.

Sollmann [4] states that the average lethal dose of morphin sulphate for guinea-pigs is about 700 mg. per kilogram when the drug is injected subcutaneously. According to our experience, however, the dose is appreciably less than this during the winter and early spring, the time when our experiments were carried out. Injected in the form of a 1 per cent. solution in saline, the minimum fatal dose at this time was

found to be about 500 mg. per kilogram. Two pigs succumbed after a dose of 400 mg. per kilogram, but this appears to be exceptional.

Salant and Rieger [2] found that the average minimum lethal dose of caffein by subcutaneous injection into guinea-pigs was from 200 to 240 mg. per kilogram of body weight; while doses of 100 to 120 mg. per kilogram caused "no manifestation of nervous or muscular disturbance nor any departure from the normal in respiratory activity." To eliminate the possibility of a variation according to season or diet (our experiments were carried out in November), a few guinea-pigs were given

TABLE 3.—*Lethal Dose of Morphin and of Caffein Alone and in Combination Given in Subcutaneous Injection into Guinea-Pigs*

Weight of Pig in Kg.	Morphin in Mg. per Kg.	Caffein in Mg. per Kg.	Result
0.455	350	0	Survived
0.240	400	0	Survived
0.330	400	0	Died
0.390	400	0	Died
0.415	400	0	Survived
0.570	400	0	Survived
0.405	400	0	Survived
0.545	400	0	Survived
0.490	450	0	Survived
0.770	450	0	Survived
0.595	450	0	Survived
0.490	450	0	Survived
0.695	450	0	Survived
0.600	500	0	Died
0.610	500	0	Died
0.235	500	0	Died
0.340	500	0	Died
0.555	500	0	Died
0.555	500	0	Died
0.405	550	0	Died
0.360	550	0	Died
0.420	0	100	Survived
0.360	0	100	Survived
0.500	0	270	Survived
0.475	0	300	Survived
0.435	0	330	Died
0.265	500	100	Died
0.500	500	100	Died
0.475	400	100	Died
0.250	400	100	Died
0.500	330	100	Died
0.520	330	100	Died
0.451	250	100	Survived

caffein subcutaneously in the form of a 1 per cent. solution in saline. In agreement with the observations of Salant and Rieger, it was found that a dose of 100 mg. per kilogram produced no detectable change in the pigs; and it was necessary to administer more than 300 mg. per kilogram before death of the animal ensued. It seems fair to assume, therefore, that 100 mg. of caffein per kilogram injected subcutaneously into guinea-pigs is by itself nontoxic. In a third series of pigs, however, it was found that the injection of this amount of caffein appreciably lowered the resistance of the animals to morphin intoxication, the average lethal dose of morphin sulphate for the pigs receiving 100 mg. of caffein per kilogram being reduced from 500 to 330 mg. or less per kilogram. These results are given in Table 3.

EXPERIMENTS WITH MORPHIN AND CAFFEIN PERFORMED ON WHITE MICE

In the next experiments, white mice were utilized. According to Hunt [5] the average minimum fatal dose of morphin sulphate for white mice is 600 mg. per kilogram, but the resistance of the animals is influenced much by adventitious factors. During November, we found

TABLE 4.—*Lethal Dose of Morphin and of Caffein Alone and in Combination Given in Intraperitoneal Injection into White Mice*

Weight of Mouse in Kg.	Morphin in Mg. per Kg.	Caffein in Mg. per Kg.	Result
17.3	300	0	Survived
15.5	300	0	Survived
24.0	300	0	Died
20.0	350	0	Survived
16.5	350	0	Survived
19.0	350	0	Died
17.0	350	0	Died
20.0	350	0	Died
17.5	400	0	Survived
20.0	400	0	Survived
18.0	400	0	Died
14.5	450	0	Died
19.5	450	0	Died
16.0	500	0	Died
25.0	500	0	Died
22.5	550	0	Died
24.0	550	0	Died
25.2	0	160	Survived
19.8	0	160	Survived
22.5	0	180	Survived
21.1	0	180	Survived
17.7	0	180	Survived
23.0	0	180	Survived
18.5	0	180	Survived
18.0	0	180	Died
25.4	0	200	Survived
23.0	0	200	Survived
12.5	0	200	Survived
30.3	0	200	Died
20.0	0	200	Died
16.5	0	200	Died
15.0	0	220	Died
16.5	0	220	Died
21.0	0	250	Died
16.5	0	250	Died
24.0	300	150	Survived
17.6	300	150	Survived
25.3	300	150	Died
22.0	330	120	Died
15.5	330	120	Died
23.0	330	120	Died
24.0	330	110	Died
18.0	330	110	Died

that the minimum lethal dose for the animals kept on an oat diet was in the neighborhood of 350 mg. per kilogram, no mouse surviving a dose of 450 mg. of morphin sulphate per kilogram. As in the experiments on guinea-pigs, a 1 per cent solution of morphin sulphate in saline was employed; but with the mice, the injections were made intraperitoneally.

5. Hunt, Reid: The Effects of a Restricted Diet and Various Diets Upon the Resistance of Animals to Certain Poisons, Bull. 69, Hyg. Lab., U. S. P. H. S.

Hale[6] puts the minimum lethal dose of "caffein citrate" at 700 mg. per kilogram in white mice, when the method of administration is subcutaneous. Using a 1 per cent. solution of the free base in saline and making the injections intraperitoneally, we placed the minimum fatal dose at about 200 mg. per kilogram. Hale's dose is equivalent to about 350 mg. per kilogram; the difference between this amount and that found necessary by us is probably referable to the different method of administration.

When from 55 to 75 per cent. of the estimated minimum lethal dose of caffein is injected into white mice, there appears to be a definite reduction in the resistance of these animals to morphin poisoning. As previously mentioned, the average minimum lethal dose of morphin sulphate alone for white mice when injected intraperitoneally is about 350 mg. per kilogram; but when caffein is used in the amounts mentioned, the lethal dose of morphin seems to be between 300 and 330 mg. per kilogram. When morphin alone was used, two of the three mice receiving doses of 400 mg. of morphin sulphate per kilogram survived; in the caffein-morphin series, no mouse survived a dose of 330 mg. These results on mice are given in Table 4.

COMMENT

From these experiments, it appears that caffein, either in large amounts or in doses quite comparable to those sometimes employed clinically, instead of proving an effective antidote for morphin poisoning, actually exerts an unfavorable action. This is in harmony with the results of Hale[6] and of Pilcher,[3] the former finding that caffein appeared to enhance the toxicity of acetanilid, and the latter that caffein lessened the chances of recovery from severe ethyl alcohol poisoning. It was suggested in both these cases that the undesired synergism was exerted on the heart; in fact, Hale secured tracings which supported this view for caffein and acetanilid. A similar depressant action on the heart appears to be the explanation for the unfavorable results with caffein and morphin; the evidence in support of this will be presented elsewhere in a more technical discussion of the problem.

That a deleterious action would result from the use of caffein in a human being suffering from morphin poisoning cannot be stated positively. Quantitatively, there is a vast difference in the action of morphin on man and on any of the animals used in this investigation. It is possible that the respiratory center of man is peculiarly sensitive to the action of morphin; so that death in human beings would result from doses of morphin which affect the circulation little or not at all; while,

6. Hale, Worth: The Influence of Certain Drugs upon the Toxicity of Acetanilide and Antipyrine, Bull. 53, Hyg. Lab., U. S. P. H. S.

on the other hand, in the lower animals, the larger doses necessary to cause death involve the heart muscle also. If this is the case, it is conceivable that caffein, by combating the respiratory depression which is the chief or sole factor in clinical morphin poisoning, may be of value as a physiologic antidote. It is generally assumed that morphin is practically free from a depressant action on the circulation when used clinically; so far as we are aware, no observations have been reported concerning the condition of the heart in clinical morphin poisoning. It would be of great interest to ascertain whether large doses of morphin depress the heart in human beings; such knowledge would enable us to draw more satisfacotry conclusions regarding the rôle of caffein in the treatment of clinical poisoning by morphin sulphate.

CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE

II. HYPERTENSION *

H. S. FEIL, M.D., AND L. N. KATZ, M.D.

CLEVELAND

The phases of ventricular systole have been fully studied in the experimental animal under various dynamic conditions. Wiggers,[1] in a recent critical report, not only analyzed the effect of general arterial constriction, but also studied the results of aortic compression at different points. The isometric period under increased arterial resistance was, in most cases, unaltered, although occasionally it was shortened; and when the aorta was compressed near the semilunar valves, the isometric period was lengthened. The ejection phase was shortened by increasing the arterial resistance except when it was associated with considerable systolic retention in the ventricle. Under the latter conditions, the ejection phase was lengthened. On this basis of experimental data we might anticipate certain clinical findings in hypertension. With an efficient heart, elevation of blood pressure should cause no change or slight lengthening of the isometric period and a shortening of the ejection phase. In a failing heart, with its attendant venous congestion, lengthening of both phases should follow. How closely anticipated effects follow dynamic changes in man may be judged from our observations.

Weitz [2] studied the duration of the cardiac phases in man under various pathologic conditions. He utilized the apex beat in measuring these periods—a method that is not free from error. In the few hypertension cases that he analyzed he noted an occasional lengthening of the isometric period, with the ejection phase shorter than the normal at corresponding rates. Meakins [3] noted that left ventricular preponderance and high blood pressure were frequently associated with a prolonged S-T interval. Fenn,[4] in a recent study, found systole unchanged in many cases of hypertension, but noted a distinct lengthening in others. As he used only the Q-T interval, his results hold only for total systole or, more precisely, for electrical systole.

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* From the Medical Clinic of Western Reserve University at City Hospital.

1. Wiggers, C. J.: Am. J. Physiol. **56**:415, 1921.
2. Weitz, W.: Deutsch. Arch. f. klin. Med. **127**:325, 1918.
3. Meakins, J. C.: Prolonging of "S-T" Interval of Ventricular Complex as Shown by Electrocardiograph, Arch. Int. Med. **24**:489 (Nov.) 1919.
4. Fenn, G. K.: Studies in Variation of Length of Q-R-S-T Interval, Arch. Int. Med. **29**:441 (April) 1922.

The method employed in our present observations was the same as that described in a previous paper.[5] Figure 1 is a typical example of the records from which the duration of systole and its component phases were obtained. The upper curve inscribes the heart sounds, the middle curve the subclavian arterial pulse, and the electrocardiogram (Lead II) is below. In all, twenty-four cases were studied. Clinical observations and blood pressure readings were made at the time of the graphic registration. These data are tabulated in Table 1, arranged according to heart rate (Column 3), which in this series ranged from 46 to 127 beats per minute with a corresponding cycle length (Column

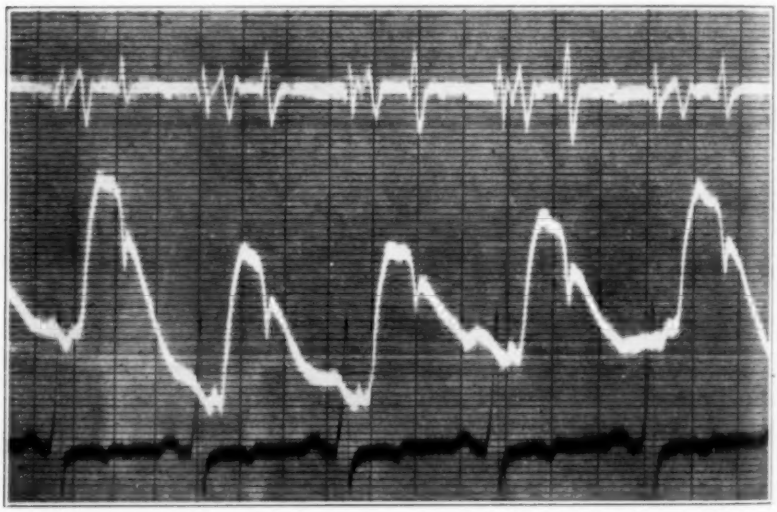

Fig. 1.—Simultaneous record of heart sounds (upper curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve), used in this series. The duration of the component phases of cardiac systole were determined by the method described in a previous paper. Time in fifths of a second.

4) varying from 0.392 of a second in Case 1 to 1.572 of a second in Case 24. In Columns 5, 6, 7 and 8 are given respectively the durations of diastole, total systole, isometric contraction and systolic ejection. The time relation of these phases to the heart rate are, with one or two exceptions, the same as in the normal series reported by us elsewhere.[5]

5. Katz, L. N., and Feil, H. S.: Clinical Observations on the Dynamics of Ventricular Systole. I. Auricular Fibrillation, Arch. Int. Med. **32**:672 (Nov.) 1923.

ISOMETRIC PERIOD

An analysis of Table 1 shows that the isometric period usually falls within the normal range, that is, from 0.03 to 0.07 of a second in many instances, namely, Cases 3, 4, 5, 6 (a), 6 (b), 6 (c), 6 (d), 8 (a), 9, 12, 14 (a), 14 (b), 16, 18 and 19, but in all these cases it is in the upper limits of normal. In other persons it is slightly longer (namely, Cases 1, 2, 7, 10, 11, 17 and 22), and in still others it is distinctly longer than normal (namely, Cases 13, 15, 20, 21, 23 and 24). An example of a record in which the isometric period varied from 0.07-0.09 of a second is shown in Figure 1.

In Table 1, we have indicated in Columns 10, 11, 12, 13 and 14 our clinical observations on the patient (age, systolic and diastolic blood pressure, etc.). A further study of this part of the table shows that this lengthening in hypertension bears no definite relation to the age, the height of either the systolic or diastolic blood pressure, the condition of the arteries, the degree of failure or the cause of the hypertension. Like the isometric phase in normal persons, it is independent of the heart rate and the duration of the other cardiac phases. The independence of the isometric period in regard to these factors confirms the opinion expressed before [5] that its duration depends primarily on the physiologic condition of the myocardium and is therefore an index of the rate of contraction of the heart.

EJECTION PHASE

When the duration of ejection in Table 1 is compared with the theoretical value obtained as we explained in a previous paper (compare Columns 8 and 9) one notes that in most instances the ejection period is less than normal, that is, the difference between Column 8 and Column 9 is greater than 0.05 of a second (namely, Cases 3, 4, 5, 6 (a), 6 (b), 6 (c), 6 (d), 7, 8 (b), 9 (b), 10, 14 (a), 14 (b), 17, 20, 21, 22 and 24). This abbreviation of ejection is illustrated in Figure 1, in which the difference between actual systole and the calculated systole is 0.09 of a second. In several this difference falls within the normal range (namely, Cases 1, 2, 11, 12, 13, 15, 16, 19 and 23), and in Case 18 it is distinctly longer than normal. When the relative shortening was analyzed from the point of view of the other variables (that is, height of systolic and diastolic blood pressure, condition of the palpable arteries, etiology of the hypertension and age of the patient) it was found to be unrelated to any of them, but it did bear a definite relation to the degree of cardiac failure, as shown in Table 2. For example, eight had a relatively reduced ejection. In fact, in Cases 9 and 14 (a) and (b) this occurred despite the lowering of the blood pressure to normal limits—the result of cardiac failure. In eleven patients without

TABLE 1.—*Duration of Systole and Its Phases in Hypertension*

1 Case	2 Number of Beats Measured	3 Heart Rate (60/C)	4 Duration of Cycle		5 Duration of Diastole		6 Duration of Systole		7 Duration of Isometric Contraction		8 Duration of Systolic Ejection		9 Calculated "S" from Formula $S=\sqrt{0.31\,C}$	10 Etiology of Hypertension	11 Age	12 Blood Pressure		13 Sclerosis of Palpable Arteries	14 Degree of Cardiac Failure
			Average	Deviation from Average	Average	Deviation from Average	Average	Deviation from Average	Average	Deviation from Average	Average	Deviation from Average				Maximum Systolic	Minimum Diastolic		
1. R. Ti.	5	127	0.470	+0.075 −0.078	0.175	+0.067 −0.030	0.275	+0.029 −0.028	0.081	+0.014 −0.019	0.194	+0.021 −0.019	0.213	D.H.S.	65	162	104	++	−
2. C. S.*.....	8	117	0.510	+0.014 −0.010	0.257	+0.007 −0.011	0.253	+0.011 −0.006	0.079	+0.007 −0.006	0.174	+0.011 −0.006	0.221	Neph.	10	235	175	−	−
3. J. M.	19	115	0.522	+0.016 −0.015	0.216	+0.013 −0.010	0.306	+0.024 −0.016	0.047	+0.014 −0.014	0.159	+0.026 −0.022	0.224	Neph.	22	158	158	−	+
4. H. Li.	7	114	0.525	+0.130 −0.180	0.202	+0.072 −0.119	0.323	+0.030 −0.028	0.062	+0.019 −0.011	0.161	+0.024 −0.044	0.225	D.H.S.	72	210	120	+++	+++
5. M. O'N. ...	7	114	0.527	+0.010 −0.011	0.336	+0.007 −0.008	0.191	+0.015 −0.017	0.062	+0.011 −0.009	0.129	+0.004 −0.018	0.225	D.H.S.	29	198	160	±	++
6(a). B. B. ..	9	113	0.531	+0.036 −0.035	0.337	+0.006 −0.007	0.194	+0.006 −0.010	0.064	+0.008 −0.009	0.130	+0.007 −0.010	0.226	D.H.S.	42	190	146	+	+++
6(b). B. B. ..	8	110	0.548	+0.006 −0.006	0.245	+0.010 −0.002	0.302	+0.006 −0.005	0.062	+0.002 −0.004	0.140	+0.004 −0.004	0.230	D.H.S.	43	190	140	+	+++
7. B. S.†.....	14	105	0.567	+0.063 −0.059	0.341	+0.006 −0.055	0.226	+0.011 −0.009	0.080	+0.009 −0.010	0.146	+0.008 −0.007	0.233	D.H.S.	54	220	136	−	−
8(a). J. Wi. .	22	101	0.596	+0.025 −0.0 8	0.294	+0.032 −0.025	0.302	+0.014 −0.021	0.063	+0.021 −0.014	0.139	+0.026 −0.032	0.239	D.H.S.	52	240	146	++	+++
9. E. S.	12	101	0.597	+0.068 −0.038	0.371	+0.080 −0.062	0.226	+0.037 −0.029	0.058	+0.020 −0.017	0.168	+0.017 −0.017	0.239	D.H.S.	46	112	86**	+	++++
10. A. Wo.‡...	6	99	0.604	+0.004 −0.004	0.342	+0.008 −0.014	0.262	+0.016 −0.007	0.073	+0.006 −0.010	0.189	+0.010 −0.010	0.241	D.H.S.	55	250	165	+	+++
11. L. O.§....	7	99	0.605	+0.005 −0.004	0.326	+0.007 −0.008	0.279	+0.005 −0.007	0.082	+0.012 −0.005	0.195	+0.0 6 −0.005	0.241	Neph.	39	190	120	−	−
12. A. Wl.¶.. .	6	99	0.607	+0.019 −0.024	0.346	+0.019 −0.018	0.261	+0.011 −0.007	0.048	+0.005 −0.006	0.213	+0.006 −0.010	0.241	D.H.S.	42	230	150	−	−
13. W. K.*.....	5	96	0.621	+0.011 −0.008	0.282	+0.007 −0.007	0.339	+0.009 −0.013	0.132	+0.007 −0.003	0.207	+0.003 −0.005	0.244	Neph.	27	210	140	−	−

14(a) J. Wa.	19	96	0.625	+0.026 −0.018	0.474	+0.025 −0.014	0.301	+0.02 −0.01	0.030	+0.02 −0.01	0.181	+0.01 −0.01	0.245	D.H.S.	52	190	95**	±	−
8(b). J. Wi. .	5	90	0.657	+0.004 −0.005	0.377	+0.003 −0.005	0.280	+0.006 −0.003	0.035	+0.003 −0.005	0.187	+0.004 −0.004	0.251	D.H.S.	52	200	140	+ +	+ + +
6(c). B. B. ...	6	89	0.670	+0.007 −0.005	0.457	+0.008 −0.005	0.213	+0.005 −0.006	0.071	+0.008 −0.006	0.142	+0.010 −0.003	0.254	D.H.S.	43	190	140	+	+ + +
6(d). B. B. .	6	88	0.678	+0.022 −0.036	0.425	+0.021 −0.023	0.243	+0.020 −0.013	0.055	+0.021 0.007	0.188	+0.006 −0.006	0.256	D.H.S.	43	160	120	+	+ + +
15. F. B.	6	87	0.687	+0.014 −0.008	0.366	+0.014 −0.002	0.321	+0.016 −0.017	0.054	+0.006 −0.005	0.227	+0.019 −0.011	0.257	D.H.S.	30	165	130	−	−
16. A. L.	6	84	0.715	+0.004 −0.002	0.436	+0.004 −0.011	0.280	+0.012 −0.004	0.096	+0.010 −0.014	0.223	+0.011 −0.011	0.262	Neph.	37	210	140	±	+ + + +
17. A. S.	5	82	0.729	+0.017 −0.035	0.450	+0.018 −0.008	0.279	+0.033 −0.013	0.078	+0.022 −0.011	0.261	+0.004 −0.014	0.265	D.H.S.	25	170	100	−	−
18. N. R.	5	80	0.753	+0.011 −0.022	0.405	+0.015 −0.014	0.348	+0.009 −0.009	0.054	+0.006 −0.008	0.294	+0.003 −0.002	0.269	D.H.S.	56	190	110	+	−
19. M. W #....	7	79	0.762	+0.038 −0.036	0.465	+0.037 −0.041	0.297	+0.015 −0.009	0.061	+0.010 −0.013	0.236	+0.012 −0.010	0.271	D.H.S.	46	165	120	−	−
14(b). J. Wa	6	78	0.773	+0.021 −0.017	0.547	+0.015 −0.006	0.226	+0.006 −0.008	0.047	+0.012 −0.009	0.179	+0.015 −0.007	0.273	D.H.S.	55	130	95**	±	+ +
20. J. D.	6	76	0.794	+0.020 −0.015	0.481	+0.013 −0.014	0.313	+0.010 −0.012	0.091	+0.003 −0.006	0.222	+0.013 −0.013	0.276	Neph.	36	190	110	−	−
21. W. Mc	8	73	0.823	+0.062 −0.065	0.508	+0.058 −0.025	0.315	+0.014 −0.042	0.100	+0.015 −0.027	0.215	+0.008 −0.015	0.281	D.H.S.	56	185	122	+ +	+
22. D. H ‖.....	13	69	0.861	+0.145 −0.308	0.567	+0.123 −0.276	0.294	+0.039 −0.032	0.079	+0.061 −0.028	0.215	+0.024 −0.030	0.288	D.H.S.	54	165	100	+	+
23. Z. Z.††.....	11	68	0.880	+0.024 −0.015	0.506	+0.027 −0.033	0.374	+0.018 −0.012	0.129	+0.016 −0.024	0.245	+0.017 −0.020	0.291	Neph.	39	220	120	+ +	+
24. A. Wi. . ..	6	46	1.295	+0.277 −0.425	0.940	+0.272 −0.418	0.355	+0.015 −0.021	0.091	+0.012 −0.011	0.264	+0.007 −0.010	0.352	D.H.S.	50	160	100	+ + +	+ +

In Columns 4, 5, 6, 7 and 8, the first figure is the average of the record measured; the plus and minus figures are the variation above and below the average.
D.H.S. indicates diffuse vascular sclerosis; Neph., chronic nephritis.

* QRST interval −0.305 (+0.007, −0.005).
† QRST interval −0.274 (+0.014, −0.008).
‡ QRST interval −0.279 (+0.017, −0.039).
§ QRST interval −0.378 (+0.017, −0.033).
¶ QRST interval −0.325 (+0.028, −0.019).
‖ QRST interval −0.339 (+0.012, −0.014).
‡‡ QRST interval −0.365 (+0.035, −0.014).
§§ QRST interval −0.374 (+0.026, −0.024).
†† QRST interval −0.400 (+0.003, −0.043).
** Blood pressure at other times much higher.

failure the duration of ejection was normal in seven instances, reduced in three and increased in one. In four cases with slight failure, ejection was reduced in three and normal in one instance.

TOTAL SYSTOLE

Like the ejection phase, total systole is abbreviated in cardiac failure. This effect is anticipated when one considers that the duration of total systole is largely determined by the length of ejection. The relation of total systole to heart rate is shown in Figure 2, which is made up of

TABLE 2.—*The Relation of the Duration of Total Systole to the Degree of Cardiac Failure*

1 Case Number	2 Heart Rate	3 Blood Pressure	4 Degree of Cardiac Failure	5 Duration of Total Systole†	6 Duration of Systolic Ejection†
1	127	162/104	None	+	N
2	117	225/175	None	N	N
7	105	220/136	None	N	—
11	99	190/120	None	N	N
12	99	230/120	None	N	N
13	96	210/140	None	+	N
15	87	165/120	None	+	N
17	82	170/100	None	N	—
18	80	190/110	None	+	+
19	79	165/120	None	N	N
20	76	190/110	None	N	—
3	115	158/128	Slight	—	—
21	73	185/122	Slight	N	—
22	69	165/100	Slight	N	—
23	68	220/130	Slight	+	N
4	114	210/120	Considerable	N	—
5	114	198/100	Moderate	—	—
6 (a)	113	190/140	Considerable	—	—
6 (b)	110	190/140	Considerable	—	—
6 (c)	89	190/140	Considerable	—	—
6 (d)	88	180/120	Considerable	—	—
8 (a)	101	240/140	Considerable	—	—
8 (b)	90	200/140	Considerable	N	—
9	101	112/ 80*	Considerable	—	—
10	99	250/165	Considerable	N	—
14 (a)	96	130/ 95*	Moderate	—	—
14 (b)	78	130/ 95*	Moderate	—	—
16	84	210/140	Considerable	N	N
24	46	160/100	Moderate	N	—

* Higher pressure obtained during stay in hospital.
† +, duration greater than normal; —, duration less than normal; N, normal duration.

all the total systoles (ordinates) plotted according to the respective cycle lengths (abscissae). The solid line is drawn to show the normal average—illustrating the theoretical relation between cycle length and total systole ($S = .31 \sqrt{C.}$). It will be seen that with the shorter cycles (above the rate of 85) systole falls below the average normal, while with longer cycles (below the rate of 85) systole tends to be slightly longer than the average normal. Cardiac failure is the only factor which we have found to alter the duration of cardiac systole consistently.

In Table 2, the cases are tabulated according to the degree of cardiac failure present. One notes that of the eleven cases without failure,

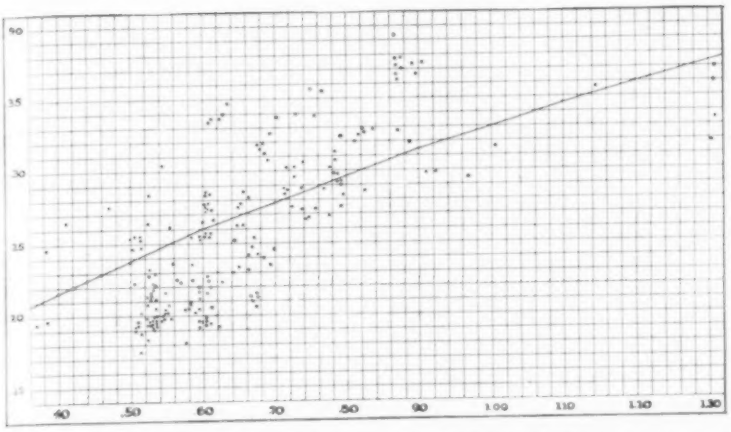

Fig. 2.—Plotting of all systoles (total). Ordinates indicate duration of systole; abscissae, cycle length. The solid line drawn to show the normal average illustrates the usual relation between cycle length and total systole. The Katz modification of Lombard and Cope's formula was used in plotting this line ($S = \sqrt{0.31\ C}$).

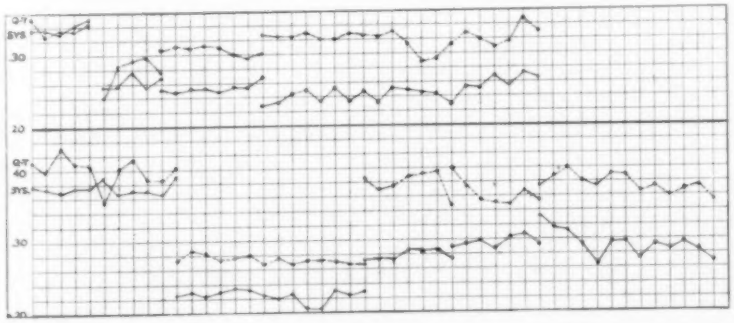

Fig. 3.—The directional agreement of the two methods of measuring ventricular systole in nine patients. The interrupted line shows the variations in systole as determined from the electrocardiogram in successive beats. The solid line indicates the systole estimated from simultaneous subclavian and heart sound records.

four have a relatively increased duration of systole (Column 5), while the other seven have a normal length. Of the four cases with slight failure, two are of normal duration, one relatively decreased and one relatively increased. Of the nine cases with failure, four have a normal duration, four a relatively reduced duration, and one case has a reduction on one occasion and is normal on another. A failing heart seems to cause an abbreviation of both total systole and the ejection phase.

The relative shortening of the ejection phase in most of these cases occurs more frequently than the reduction in total systole, owing to the prolongation of the isometric period. In other words, the relative abbreviation of ejection in some cases occurs with a normal total systole because the isometric phase is prolonged.

THE VALUE OF Q-R-S-T INTERVAL AS A CRITERION OF VENTRICULAR SYSTOLE

In nine cases, simultaneous electrocardiograms (Lead II) were made with the records of the subclavian pulse and the heart sounds. Although systole as determined by the electrocardiogram exceeded purely mechanical systole by from 0.02 to 0.08 of a second, the directional changes in systole as inscribed by the two methods were usually the same. This relationship is much closer than might be expected from animal experiments (Bartos and Burstein).[6]

COMMENT

The duration of total systole was lengthened in one third of our patients with hypertension, without signs of cardiac failure, whereas in patients with cardiac failure, systole was abbreviated in 50 per cent. The frequent association of shortening of systole in cases of hypertension dominated by failure of the circulation becomes all the more significant when our previous observations are noted, namely, that the abbreviation of systole in auricular fibrillation was greatest when cardiac failure was present. These findings are directly opposed to the results anticipated on the basis of animal experiments. The cause of this apparent discrepancy in cases of cardiac failure is probably due to the fact that our data were obtained from patients having either hypertrophied or incompetent hearts, and it is not surprising that such hearts react differently from hearts of normal animals, from which the experimental data were obtained.

CONCLUSIONS

In the study of twenty-four patients with hypertension we find dynamic changes in ventricular contraction as follows:

1. (*a*) *Patients without signs of cardiac failure.* Total systole was found to be increased in duration in one third of our cases (by 0.02

6. Bartos and Burstein: To be Published.

to 0.1 of a second). In the other two thirds there was little or no variation from the normal figure.

1. (*b*) ***Patients with signs of cardiac failure.*** Total systole was shortened in one half of the cases (by 0.01 to 0.08 of a second)—in the others, it varied little from the normal average.

2. The abbreviation of systole in the cases with failure, we believe, may be due to an altered response of the heart muscle to overloading. On the other hand, when it shows no signs of failure its dynamic reaction (lengthening of systole) is shown to be due to the prolongation of the isometric period, while the ejection phase either remains normal or is somewhat abbreviated—results anticipated from experimental data.

SARCOMA AND CARCINOMA OF THE LIVER FOLLOWING CIRRHOSIS *

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The important rôle which chronic irritations play in the etiology of malign neoplasms has been proved by numerous clinical and experimental observations. The facts are too well known to be reviewed, and I will confine myself in the present paper to the reports which deal with the primary malign tumors of the liver and their relations to chronic alterations apparently preceding their development in this organ.

It is an interesting fact that in the liver, which possesses the greatest ability to regenerate, primary malignant tumors are rare. These consist of epithelial tumors derived from the liver cells or epithelial cells of the bile ducts, and mesenchymatous tumors originating either in the stroma or in the endothelium of the blood capillaries. The epithelial tumors are comparatively more frequent than the mesenchymatous ones.

CARCINOMA OF THE LIVER

In the statistics of necropsy material, primary carcinoma of the liver occurs in from 0.02 to 0.3 per cent. of the necropsies (Goldzieher and Bokey,[1] Wheeler, Winternitz [2]). Their percentage of all cancers varies from 1.5 to 3.

The frequent combination of primary carcinoma of the liver with cirrhosis has long been known; indeed it is mentioned in the works of Hanot and Sabourin.[3] Liver cell cancers, particularly, are associated with cirrhosis (from 75 to 100 per cent.), while for biliary tumors the coincidence is about 50 per cent. (Yamagiwa [4]). The causal relation is, therefore, striking, and even since the time of Sabourin has been discussed in almost every publication dealing with cancer of the liver. Ewing,[5] Winternitz and many other observers are inclined to regard the cirrhosis as a factor predisposing to the formation of the carcinomas.

The objections raised against this assumption are twofold: (*a*) The combinations may have been a mere coincidence (Kelsh and Keiner). (*b*) The cirrhotic change assumed to precede carcinoma may, on the

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1. Goldzieher and Bokey: Virchows Arch. f. path. Anat. **203**:75, 1911.
2. Winternitz: Johns Hopkins Hosp. Rep. **17**:142, 1916.
3. Sabourin: Thése, Paris, 1881.
4. Yamagiwa: Virchows Arch. f. path. Anat. **206**:437, 1911.
5. Ewing: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

contrary, be a consequence (Markwald,[6] Wegelin[7]). The great number of observations that have been reported rule out the first contention, but it is admittedly difficult to decide exactly what changes were present in the liver before the cancer started. Did the carcinoma cause the cirrhosis by direct injury to the liver tissue or by alteration of the circulation (Markwald,[6] Wegelin[7])? The history of the case will, undoubtedly, yield some information. The determination of the presumable age of both lesions is important, and the anatomic character of the cirrhotic changes will facilitate the decision. Little cirrhosis and fully developed carcinoma speak against a predisposing influence of the former (for example, the case of F. Helvestine[8]). Of great value are observations on beginning carcinoma in cirrhotic livers (Saltykow[9]). They may distinctly show how the regeneration of liver tissue due to the cirrhosis exceeds the limits of reparation and, escaping the regulatory influence of the organism, change to an excessive and, finally, carcinomatous growth.

The frequency of cirrhosis in cases of primary carcinoma of the liver should not only be considered, but the frequency of carcinomatous degeneration in cirrhotic livers as well. Less is known about the latter phase; in future statistics dealing with primary carcinoma of the liver more attention should be given it.

In a recent report, Blumenau[10] reviewed the cause of death in 198 cases of cirrhosis of the liver (0.5 per cent. of all necropsies). He found that primary carcinoma of the liver had occurred in 3.5 per cent. of them. Based on this relatively small statistical material, it may be said that primary cancer of the liver is ten times more frequent in persons suffering with cirrhosis of the liver than in those with other lesions.

Guyders and Straub recently reported that primary carcinoma of the liver occurs frequently among the Japanese and Chinese in cases of cirrhosis. Appel,[11] in six carcinomas in natives of Kamerun, found primary tumors located in the liver four times. Cirrhosis was present in each of these cases, and the author discussed the importance of parasitic infections of the liver in this connection. Pirie[12] has also mentioned cirrhosis as a predisposing factor in the numerous primary cancers of the liver in the natives of South Africa. Several authors

6. Markwald: Virchows Arch. f. path. Anat. **144**:29, 1896.
7. Wegelin: Virchows Arch. f. path. Anat. **179**:91, 1905.
8. Helvestine: J. Cancer Res. **3**:275, 1918.
9. Saltykow: Sarcoma and Carcinoma of Liver, Cor. Bl. f. schweiz. Aerzte **44**:385, 1914.
10. Blumenau: Arch. f. Verdauungskrankh. **27**:1, 1920.
11. Appel: Arch. f. Schiffs-und Tropenhygiene **29**:309, 1921.
12. Pirie: M. J. South Africa **17**:87, 1921.

(Bamberg,[13] Loehlein,[14] Necke,[15] Modena[16] Dippelt[17]) have found cancer of the liver associated with echinococcus.

In the majority of cases observed in this country and in Europe, the cirrhosis associated with carcinoma represented the anatomic type of the atrophic or annular cirrhosis (so-called alcoholic cirrhosis). Some authors found the preceding cirrhosis to be syphilitic in origin (Yamagiwa[4]).

In animals, primary tumors of the liver seem to be rare. Carcinoma of the liver has been observed in cows, almost invariably connected with severe parasitic biliary cirrhosis (Delafield and Prudden[18]).

In material from ten thousand mice of all ages Slye, Holmes and Wells[19] found twenty-eight primary tumors of the liver. All were liver cell adenomas, three showing malignant structure, none of which were associated with cirrhotic changes. According to the authors, the mouse liver does not show cirrhosis. A questionable adenocarcinoma of the liver in a mouse was reported by Shigemitsu Itami.[20]

SARCOMA OF THE LIVER

Approximately forty-eight true primary sarcomas of the liver have been reported to date. To the list given by Terplan[21] should be added the cases of Hektoen,[22] Rolleston and Trevor,[23] Hedren,[24] Dubs,[25] Morrow and McKinstry[26] and Goldstein.[27]

Some of the tumors reported as primary sarcoma of the liver must be excluded because they were either not sarcoma or not primary sarcoma of the liver. The round cell tumors of the liver associated with similar tumors of the suprarenals and observed only in early childhood are, according to recent investigations, not sarcoma but epithelial tumors derived from indifferent sympathetic nerve cells (neuroblastoma) (Landau's[28] bibliography). Whether primary melano-

13. Bamberg, quoted by Winternitz, Footnote 2.
14. Loehlein: Verhandl. d. deutsch. path. Gesellsch. **13**:320, 1909.
15. Necke, quoted by Winternitz, Footnote 2.
16. Modena: Pathologica **6**:833, 1913.
17. Dippelt, quoted by Winternitz, Footnote 2.
18. Delafield and Prudden: Text Book of Pathology, Ed. 12, Ann Arbor, Mich., George Wahr.
19. Slye, Holmes and Wells: J. M. Res. **33**:171, 1915.
20. Itami, Shigemitsu: J. Cancer Res. **3**:275, 1918.
21. Terplan: Centralbl. f. path. Anat. **31**:453, 1920.
22. Hektoen: Trans. Chicago Path. Soc. **2**:137, 1896-1897.
23. Rolleston and Trevor: J. Path. & Bacteriol. **15**:247, 1911.
24. Hedren, quoted by Saltykow, Footnote 2.
25. Dubs: Deutsch. Ztschr. f. Chir. **138**:1, 1917.
26. Morrow and McKinstry: Brit. M. J. **2**:378, 1919.
27. Goldstein: Internat. Clin. **2**:73, 1921.
28. Landau: Frankfurter Ztschr. f. Path. **2**:26, 1912.

sarcoma of the liver exists is at least doubtful. The cases without complete necropsy cannot be accepted (F. R. Hager [29] and others).

What are the relations of the primary sarcomas of the liver to cirrhosis? Rolleston and Trevor, describing an angiosarcoma in a cirrhotic liver, said: "Primary sarcoma of the liver is far from common, and when associated with cirrhosis, is distinctly rare." They found six cases in the literature which represented sarcomas in cirrhotic livers. Since their article appeared, seven more cases have been reported (Loehlein,[14] Kothny,[29a] Hachfeld,[30] Kahle,[31] Hedren,[24] Saltykow.[32] Thus 29 per cent. of the known cases of sarcoma of the liver were combined with cirrhosis.

Several authors express the opinion that the cirrhosis may have played a predisposing rôle in the formation of the sarcoma (Rolleston and Trevor,[23] Kahle [31]).

Hedren's spindle cell sarcoma was located in a liver with syphilitic cirrhosis. The cases of Goldstein,[27] Dubs [25] and de Vecchi [33] are of interest in this connection. Goldstein reported a spindle cell sarcoma in the liver of a man 38 years of age, arising from the wall of a chronic abscess. Dubs reported the case of a girl 26 years of age, who died six months after an injury to the liver. He found a primary spindle cell sarcoma of the liver, 30 by 30 by 25 cm. in diameter, and he discussed the possibility of a relationship between trauma and sarcoma. De Vecchi saw a similar tumor derived from the wall of an echinococcus cyst.

The experimental work of Bullock and Rohdenberg,[34] and Bullock and Curtis [35] proved the possibility of producing sarcomas in the liver in rats by infection with the eggs of *Taenia crassi-collis*. But connective tissue of rats seems to be much more apt to undergo sarcomatous transformation than that of human beings.

The hemangio-endothelioma of the liver is derived from the endothelial cells of the capillary vessels of the vena portae. I have previously mentioned that this tumor was sometimes found in cirrhotic livers (Kahle, bibliography; E. Schlesinger [36]).

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29. Hager, F. R.: The Surgical Clinics of Chicago **3**:121, 1919.
29a. Kothny: Frankfurter Ztschr. f. Path. **10**:20, 1912.
30. Hachfeld: Inaugural Dissertation, Halle, 1914.
31. Kahle: Virchows Arch. f. path. Anat. **226**:44, 1919.
32. Saltykow: Beginning Carcinoma of Liver, Verhandl. d. deutsch. path. Gesellsch. **15**:292, 1912.
33. De Vecchi: Soc. Med. Chir. di Bologna **6**, June, 1908.
34. Bullock and Rohdenberg: J. M. Res. **28**:477, 1913; Rohdenberg and Bullock: J. Cancer Res. **1**:81, 1916.
35 Bullock and Curtis: Proc. New York Path. Soc. **20**:149, 1920.
36. Schlesinger: Inaugural Dissertation, Frankfurt, 1920.

SARCOCARCINOMA OF THE LIVER AND SARCOMA AND CARCINOMA IN THE SAME LIVER

There remain sarcocarcinoma of the liver and the separate formation of carcinoma and sarcoma in the same liver. Reports of sarcocarcinoma were published by Lubarsch [37] and Saltykow. Both tumors were found in cirrhotic livers.

Of great interest are the rare observations of two different malignant tumors—of a sarcoma and of a carcinoma—in different parts of the same liver. I am aware of but two cases so far reported.

The first case is that of Dominici and Merle.[38] A man, aged 56, died a short time after his admittance to the l'Hotel-Dieu in Paris. Alcoholism was mentioned in his history. The liver showed a definite atrophic cirrhosis and was interlaced by tumor masses. There were metastases in the lower lobe of the right lung, in the head of the pancreas and in the suprarenals. Microscopic examination revealed old cirrhotic changes in the liver. There was adenomatous hyperplasia of the liver tissue, which passed over directly to carcinomatous areas. In these places the liver cells had lost their structure entirely and appeared as small cells of embryologic character. In a part of the liver with less cirrhosis a spindle cell sarcoma was detected. The metastases were formed by sarcomatous tissue.

The authors conclude their observation with the remark: "Ce cas anatomo-pathologique est un des examples les plus typiques que l'on puisse trouver d'association entre les processus de tumeur et des processus d'inflammation chronique."

The other case was observed by Saltykow. The patient was a man aged 62. Nothing is reported about the history. At necropsy two tumors were found besides distinct atrophic cirrhosis. The larger tumor, 20 by 16 by 9 cm. in size, was a typical spindle cell sarcoma; the smaller tumor, 3 cm. in diameter, was an early liver cell carcinoma.

To these two cases I wish to add a third.

REPORT OF A CASE

History.—A white man, aged 64, a traveling salesman, said he did not have a chancre. He had had gonorrhea several times years ago. He had been a hard drinker in former years. The clinical diagnosis of cirrhosis of the liver was first made fifteen years ago. About three months before admittance to the hospital the patient had had dull pains in the epigastrium and belching of gas. He had no appetite, was usually constipated and the stools had an offensive odor. When the patient was brought to the hospital, he seemed to be rather dull, and he was not responsive to questions. He passed only a few drops of an almost black urine. He died two days later.

37. Lubarsch: Zur Lehre von den Geschwulsten, 1899.
38. Dominici and Merle: Arch. de med. exper. et d'anat. path. **21**:136, 1909.

Necropsy (Sixteen hours after death).—The body was that of a fairly well nourished man, 175 cm. long. The skin and eyeballs were distinctly yellow. The abdomen was distended.

The situs of the abdominal organs was normal. The bladder was empty. The lungs were voluminous; their edges appeared rounded. The lung tissue in all parts was of normal air content and hyperemic.

The heart was of normal size, covered partly with fat tissue, and very loose. In its cavities were postmortem blood clots. The myocardium was grayish brown and friable. The endocardium over the papillary muscles was thickened. The valves were unaltered. There were little calcified plaques in the ascending part of the aorta.

The liver was covered partly by the adherent omentum and firmly attached to the diaphragm. Its form was very irregular. The right lobe was almost entirely replaced by a spherical mass, 17 by 12 by 14 cm. in size. On the

Fig. 1.—Cross section through the liver; *1*, sarcoma; *2*, carcinoma.

surface not covered by the diaphragm larger and smaller nodes of white or reddish white color were prominent. The left lobe was small, and its surface showed small, flat, grayish brown nodules with lighter strips between them. There was a single larger node softer and more yellowish in color.

Cross sections (Fig. 1) through the liver showed that the right lobe consisted of a dense and faintly reddish stained tissue. Wavy bands of reddish white alternated with more grayish ones. This tissue continued into the muscles of the diaphragm as tortuous bands. The center of the lobe was formed by an irregular cavity filled with a thick reddish gray, cheesy material. There was little liver tissue left around the dense masses.

The left lobe revealed, on the cut surface, a mosaic-like structure. Round, grayish brown nodules were separated by firm, grayish white bands. The diameters of the soft yellow nodule mentioned above were 2 by 1 cm. It was located just below the capsule and was formed by a homogeneous tissue

(Fig. 2). Adjacent to it several smaller oval areas of a similar appearance could be observed. The wall of the gallbladder was partly replaced by white or grayish white nodules which bulged into the cavity. The mucosa was yellow and ulcerated over the nodules. A yellowish gray mucus filled the cavity. There were no calculi.

The vena portae and its branches seemed to be free, as did also the arteria hepatica and the vena hepatica. There was no enlargement of the lymph glands.

The spleen was somewhat enlarged, its weight was about 200 gm. Its capsule showed singular thickened areas. The pulp was red and soft, but the structure was distinct.

The suprarenals were colliquated and changed to a brown and pulpy mass.

The kidneys were embedded in fat tissue. Their surface showed small cysts; in the left kidney there was a larger cyst, 3 cm. in diameter. The kidneys were dark grayish red, and in the medulla, small glittering, whitish stripes were noted.

In the colon were claylike masses. The blood vessels of the mucosa of the stomach were somewhat dilated.

Microscopic Examination.—Left Lobe of the Liver: Round and oval islands of liver tissue varying in size from the fourth of a normal acinus to its twofold or threefold diameter were surrounded by connective tissue. In these islands, the normal structure of the acini was gone. The central vena was distorted and some acini had two or three central venae. The columns of the liver cells ran in various directions without distinct arrangement around a central blood vessel. The majority of the liver cells themselves were more or less altered. Many of them were smaller than normal; their nuclei were poorly stained or they were shrunken and dark. The cytoplasm contained yellow-brown granules of iron-free pigment. Many cells showed smaller or larger fat droplets; some cells were filled with fat which stained yellowish red with Sudan III and pink with Nile-blue sulphate. At the periphery of the acini, where proliferating connective tissue invaded the acini, single liver cells became isolated and showed extreme fatty degeneration. The fat gave double refraction and stained violet with Nile-blue sulphate.

Between the degenerated and atrophic liver cells, larger and well preserved cells were intercalated. Their protoplasm was homogeneous, and their nuclei had a distinct chromatin network with a round nucleolus. Cells with two nuclei were frequent. Sometimes the nuclei were large and irregular. Their edges were notched and their chromatin formed clumpy, dark masses.

In some places within the areas of the liver cells, an increased amount of connective tissue was present. Using Mallory's stain and silver impregnation, it was found that these fibers were derived from the thickened and clotted reticular fibrils.

The septums separating the areas of liver tissue were from 0.5 to 2 cm. in thickness. They were formed by dense fibrous tissue with a few small and dark nuclei. A larger number of cells occurred in those parts of the fibrous tissue in which the bile ducts proliferated. Sometimes the proliferation of the bile ducts was so pronounced that adenoma-like formations resulted. There were areas, 1.5 mm. in diameter, consisting almost entirely of larger and smaller bile ducts. A circumscribed increase of cells was also formed by accumulations of round cells. They were located at the periphery of the septums and often infiltrated the adjacent liver tissue. Here the liver cells, as described above, underwent intensive fatty degeneration, and itinerant cells with fat granules joined the lymphocytes of the infiltrates.

The subcapsular soft node of the left lobe was formed by a tissue very irregular in arrangement and of cells that resembled liver tissue (Fig. 2). There were rows of cells lining capillary vessels with a distinct endothelium. The cells were small, cuboid, packed closely together, with very dark and wrinkled nuclei. In the same rows there were large polyhedral cells. The nuclei of these cells were partly round and showed a chromatin structure like

that in the nuclei of normal liver cells. Often the nuclei were extremely enlarged and deeply stained. Vacuoles distended them so that peculiar forms resulted.

There were parts wholly formed by the latter type of cells. The cells contained droplets of yellowish brown, iron-free pigment. It was located either in single, small vacuoles or it filled the whole body of the cell. Some cells showed a diffuse brownish color. The pigment continued as small stripes connecting the masses within the cells with homogeneous, pigmented material between them.

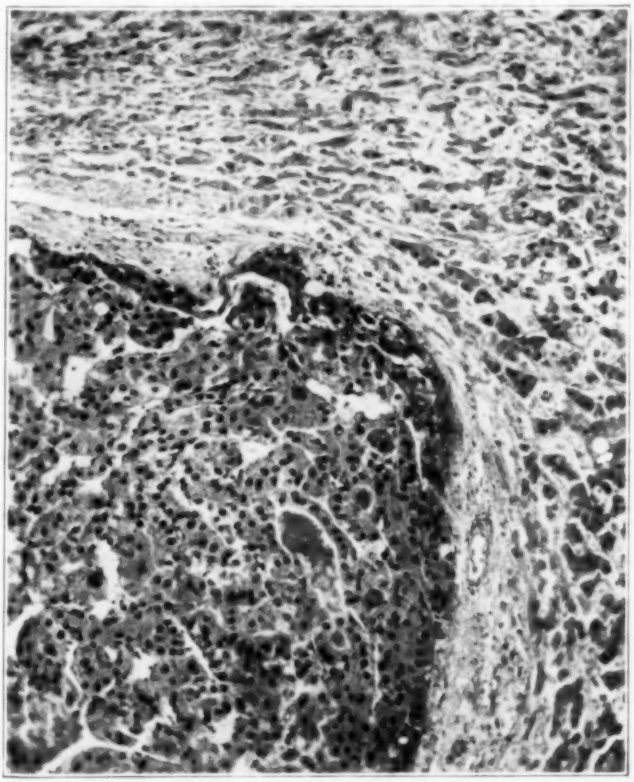

Fig. 2.—Liver cell carcinoma; tumor mass in a branch of the vena hepatica.

This pigment differed from the normal bile pigment in its consistency, being apparently more fluid, and in color paler and more yellowish. Stained with Malloy's phosphoric-molybdic hematoxylin, the normal bile appeared dark green or brown-green, while the pigment of the irregular parts took up only a pale yellowish green; the atypical liver cells appeared to have produced an atypical secretion.

Mitotic figures were rare. The proliferation of the cells seemed to be the result of amitotic division as indicated by the various stages of constriction of the nuclei.

Silver impregnation (Bielschowsky-Maresch) revealed a loose and irregular reticulum between the cells.

The center of the nodes was necrotic and contained no nuclei. Droplets of neutral fat and coarse granules of dark yellow pigment filled the necrotic cells; disintegration often occurred so that the fat and pigment became free. Besides these masses the débris contained needles of fatty acids and double refracting fat. The atypical liver tissue was not connected directly with the other parts less irregular in their structure. A small amount of fibrous tissue separated them from each other. In the vicinity of the node smaller areas of atypical

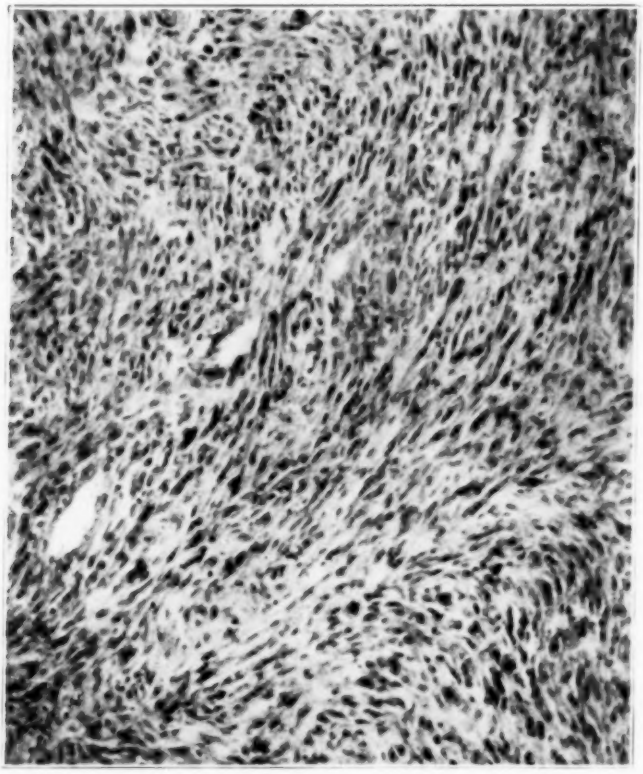

Fig. 3.—Spindle cell sarcoma.

cells were found. They were located within blood vessels as the well preserved wall of the vessels at their periphery still indicated. Sometimes the lumen of a vessel was not closed up by the cell masses, the latter being separated from the endothelium of the wall by a layer of clotted blood.

The microscopic structure of the large tumor of the right lobe of the liver could be recognized at the periphery, the central parts being necrotic. There the tumor was composed of large fusiform cells, from 70 to 100 microns in length (Fig. 3), forming bundles which interlaced in various directions. The majority of the nuclei were spindle shaped and dark, with a dense chromatin meshwork.

Some nuclei were larger and more irregular. They were bent, kidney-like or horseshoe-like, or they were segmented and tortuous. Between the fusiform cells single cells were conspicuous because of their great size and their dark nuclei.

Mitotic figures of the nuclei were frequent; in every field of the higher power magnification two or three of them could be found. Their forms were often atypical with asymmetric arrangement of the chromosomes, three or four poles, etc.

Fatty Changes.—A peculiar feature of the tumor was the result of fatty changes. All the cells contained fat droplets, even those with mitoses. Some cells had only a few small droplets; in other cells the body was filled up with fat. If the nucleus was just undergoing mitotic division, the droplets were located at the periphery of the cells in a regular wreath. In some, the fat was mixed with the chromosomes.

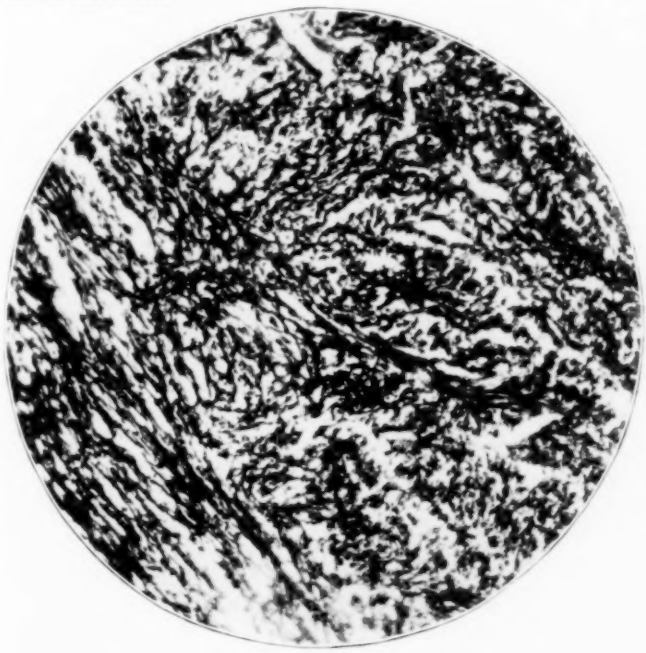

Fig. 4.—Spindle cell sarcoma; Bielschowsky's stain.

The fat stained yellowish red or orange with Sudan III. With Nile-blue sulphate, the larger droplets took up a purple color and were often surrounded by dark blue rings or dark blue granules. The droplets of medium size were violet and the small fat granules were dark blue. Fischler's microreaction for fatty acids was positive in some of the larger droplets. The membranes and granules around the larger droplets stained blue with Nile-blue sulphate and gave a black impregnation with Lorrain-Smith chromehematoxylin. Only the small droplets showed double refraction. In the necrotic parts all fat was stained pink with Nile-blue sulphate. The Lorrain-Smith impregnation was negative. There was no double refraction.

According to these findings, it can be said that the larger droplets are formed by neutral fat which often contains free fatty acids. The droplets are

surrounded by membranes of a complicated lipoid mixture. In the small droplets, cholesterol esters are present. In the necrosis, all fat is neutral fat.

Connective Tissue.—In the sections stained with hematoxylin and eosin or with van Gieson's picric acid, acid-fuchsin solution, little collagenous tissue could be seen between the fusiform cells. Using Mallory's stain for connective tissue or Bielschowsky's and Maresch's silver impregnation, the large amount of fibers which surrounded and separated the cells was astonishing (Fig. 4).

A basket-like network was formed above the cells by brushlike branches given off from the side of thicker longitudinal fibers. Toward the central parts where the tumor cells became necrotic the network of fibers was intact; it seemed even to be denser because the fibers were more closely packed together. Only near the central cavity did the fibers break up into granules and irregular segments.

The relation of the tumor to the connective tissue of the cirrhotic part: The tumor was directly connected with the cirrhotic connective tissue. The transition zone between them was rather sharp; only at a few points did the large spindle cells invade more deeply the tissue of the septums. Where the tumor bordered on liver tissue, liver cells became isolated by the tumor just as they were by the fibrous tissue of the cirrhosis. The liver cells located within the tumor were greatly altered, showing fatty degeneration, atrophy and necrosis. The framework of the old acini could still be recognized in the midst of the tumor.

The nodes in the wall of the gallbladder showed the same structure as the tumor in the right lobe of the liver. They contained large spindle cells arranged in bundles, with dark nuclei, often atypical. In some parts a considerable amount of connective tissue was elaborated by these cells. Inside the gallbladder the tumor was necrotic and stained by bile pigment. On the outside, the muscle fibers were still present, although disintegrated and compressed by the invading tumor cells.

Kidney: Few glomeruli were obliterated in the kidney. In the epithelial cells of the convoluted and straight tubules, droplets of neutral fat were found. The cyst was lined with flat epithelium and filled with homogeneous masses. There was little sclerosis in the larger arteries.

The glittering stripes in the medulla were formed by thickened and hyaline interstitial tissue. They contained groups of fat droplets. On microchemical examination it was found that the fat consisted of neutral fat, fatty acids and lime soaps.

Spleen: The malpighian bodies were small. In the pulp the reticulum was distinctly thickened. The sinuses were filled with blood. There were few lymphoid cells and plasma cells besides the erythrocytes.

Microscopic examination of the other organs revealed no important changes.

COMMENT AND SUMMARY

In the present case the clinical diagnosis of cirrhosis of the liver was made fifteen years ago. In accordance with this, the anatomic examination revealed an extensive transformation of the liver. That the cirrhosis was still progressing was indicated by the recent changes on the periphery of the acini.

The tumor in the right lobe of the liver was a typical spindle cell sarcoma. It originated in the fibrous septums between the transformed acini. It seems that the slowly progressing new formation of connective tissue had suddenly taken on an extremely rapid and destructive proliferation, the cells showing a tendency of growing around the liver acini and imitating the periacinare growth of the cirrhotic connective tissue from which they were derived.

The spindle cells of the tumor were connected by a well developed meshwork of reticular fibers, formed, no doubt, by the tumor cells themselves. Haruso Kuru [39] considers such a reticular network typical of the spindle cell sarcomas.

It is, of course, not possible to determine exactly the date when the sarcoma started. But the rapid progress of the disease during the last month of life and the great number of mitotic figures indicate that the tumor grew fast.

Primary sarcomas of the liver are not apt to produce metastases. In this case, metastases occurred only in the gallbladder. There is no doubt that the tumors of the gallbladder were secondary to the tumor in the right lobe of the liver. In a previous paper,[40] I have described the differences between primary and metastatic sarcoma of the gallbladder.

In the liver cells marked degeneration was observed which apparently had developed shortly before death. There were areas of liver cells which were free from degenerative changes; these were the zones of regeneration. In one area in the left lobe, the new formation of liver tissue had exceeded the limits of regeneration. Here the cells showed all the signs of a destructive and malignant proliferation. At the periphery the cells were small with relatively large and very dark nuclei (embryologic, Dominici and Merle [38]). Toward the center the cells became large and atypical, although they still resembled liver cells. They were arranged along capillary blood vessels and manifested an attempt at bile formation. They had invaded hepatic veins and spread out within their lumen. Because of these findings the tumor in the left lobe of the liver is called a liver-cell carcinoma (hepatoma).

It is a question whether the single atypical cells found in other parts of the liver in close connection with regenerative changes may be regarded as further centers of beginning carcinomatous growth. That would indicate a multiple origin of carcinoma. These cells were certainly not metastatic tumor cells, for they were located within the columns of the liver cells and not between them in the capillaries.

We know that atypical cells are not rare in regenerative tissue growth, and one is not justified in making a diagnosis of beginning carcinoma from a single cell. I suppose that the irregular cells in certain areas resulted from the efforts of an extensive regeneration. While the boundless destructive proliferation of the cells appeared in various parts, only in one place did it lead to the formation of a true carcinoma.

39. Kuru: Verhandl. d. deutsch. path. Gesellsch. **13**:386, 1909.
40. Jaffe: Centralbl. f. path. Anat. **29**:571, 1918.

From the clinical history and the result of the microscopic examination, we believe that in the present case the cirrhosis preceded the carcinoma as well as the sarcoma. Both tumors had developed from tissue which can be identified as of cirrhotic origin.

The connective tissue between the transformed liver acini was old scar tissue. That sarcoma may arise from scar tissue is well known (Simon [41]), and it is interesting that the majority of these sarcomas are of the spindle cell type. The cirrhosis may be regarded as having favored the formation of the sarcoma.

I have stated that the carcinoma started in regenerated liver tissue. The regeneration was due to the cirrhotic destruction of the liver, but it was, no doubt, greatly stimulated by the sarcoma which had destroyed almost the whole right lobe. Some causal relations, therefore, may have existed between the two malignant tumors.

41. Simon: Ztschr. f. Krebsf. **10**:210, 1911; Berl. klin. Wchnschr. **3**: 1914

ARTERIOSCLEROSIS AND HYPERTENSION*

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Some time ago, while making routine examinations of the eyegrounds in the medical wards, a finding of peculiar interest and of great importance was noted. A patient with typical advanced arteriosclerosis of the radial and brachial arteries had absolutely normal retinal vessels. It was assumed at the time that this was merely an accidental finding. Later, however, we observed the same phenomenon in another patient. Analyses of these two cases disclosed the fact that both patients had normal blood pressures. Among the more recent references to retinitis of circulatory disease are those of Schieck and Volhard,[1] Benedict,[2] Behan[3] and Cohen.[4] For the most part, these are descriptive of the lesions found in the retina, together with speculations on cause and effect. We were cognizant, of course, from Allbutt's writings and our own experience, that marked peripheral arteriosclerosis could occur with normal blood pressure. We were unaware, however, of any published observations on the retinal vessels in such cases. Practically the only reference to the relation between blood pressure and large and small vessel sclerosis is an indirect one by Moore,[5] who found that in twenty-one patients suffering from intrathoracic aneurysms, with an average systolic pressure of 141 mm.: "There was no evidence of any considerable disease of the retinal arteries in any case." The same author states that hypertension is the rule when retinal arteriosclerosis is present. It was felt that if our observations could be verified in a large series of cases, it would throw light on the relation between arteriosclerosis and blood pressure. Consequently, we examined as

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1. Schieck, F., and Volhard, F.: Netzhautveränderungen und Nierenleiden, Zentralbl. f. d. ges. Ophth. **5**:465-470, 1921.

2. Benedict, W. L.: Retinitis of Cardiovascular and Renal Diseases, Am. J. Ophth. **4**:495-499 (July) 1921; Retinitis of Acute Nephritis; Report of Six Cases, M. Clinics N. America **5**:275-288 (Sept.) 1921.

3. Behan, J. L.: Fundus Changes in Nephritis, J. A. M. A. **78**:1691-1694 (June 3) 1922.

4. Cohen, M.: Significance of Pathologic Changes in Fundus in General Arterial and Kidney Diseases, J. A. M. A. **78**:1694-1701 (June 3) 1922.

5. Moore: Medical Ophthalmology, Philadelphia, P. Blakiston's Son & Company, 1922.

many of these nonhypertensive peripheral sclerotic patients as we could find. To date, these have numbered fifty. In passing, it may be worth mentioning that many of these persons are old, and that cataracts or other opacities in the media are extremely common. This naturally reduces markedly the number of available cases, because the retinas in such cases cannot always be seen with sufficient clarity to pass judgment on the vessels.

It seemed desirable to contrast with these nonhypertension cases a group of patients with peripheral sclerosis who showed hypertension and, if possible, another group of hypertensive patients who did not show peripheral arteriosclerosis. We were not successful in obtaining cases of the latter type, because, while many showed no obvious sclerosis of the radials and brachials, most showed at least slight thickening and tortuosity of the temporals. It was, therefore, decided to include all of these cases in the other group of hypertensive patients. As a rule, the cases in Table 2, in which the patient's peripheral vessels are noted as slightly thickened or tortuous are those in which the obvious sclerosis is confined to the temporal vessels. There has always been a question in our minds about the importance of tortuous temporal arteries. They seem to be common in apparently normal people. In a study of this kind, however, it was deemed necessary to include them.

Our observations on the peripheral vessels were confined to the radials, brachials and temporals. No doubt, additional information might have been obtained from examination of the arteries in the legs. But for our purposes the examination of the three mentioned seemed sufficient.

In the examination of the retinal arteries, we confined ourselves largely to the two signs of arteriosclerosis that are absolute and beyond criticism. These signs are compression effects at arteriovenous crossings and irregularity of the lumen. We included also with the latter the more advanced signs of sclerosis—beading and obliteration of the red columns through increasing opacity of the wall. We felt that the other signs of sclerosis were too variable and too dependent on personal judgment of what was normal and what was pathologic.

The results of this study are embodied in Tables 1 and 2. Table 3 is a summary of Tables 1 and 2. In the first table are included fifty cases of peripheral arteriosclerosis with systolic blood pressures under 145. The peripheral sclerosis varied from slight tortuosity or thickening to beading and calcification. More than one half of these show at least "marked sclerosis." In contrast, the retinal vessels show almost no sclerosis. (This is brought out better in Tables 2 and 3.) From the arrangement of the blood pressures according to an ascending value for the systolic, it can readily be seen that there is no relation between the

height of either the systolic or diastolic pressure and the degree of sclerosis. No comparison, of course, can be made between the pressures and retinal vessel sclerosis in this group—there is so little sclerosis.

The average age in this group is 55.6 years, the extremes being 13 and 82 years. The average is probably lowered considerably by two

TABLE 1.—*Types of Sclerosis in Patients with Various Diseases* *

Case No.	Age	Diagnosis	Blood Pressure	Peripheral Vessels	Retinal Vessels
1	61	Peptic ulcer	89 / 48	++++	0
2	47	Convalescence from pneumonia	92 / 57	++	0
3	28	Diabetes	92 / 64	++	±
4	60	Aortic insufficiency, chronic nephritis	100 / 40	+++++	±
5	13	Diabetes	101 / 80	++	0
6	65	Chronic bronchitis, arthritis	102 / 50	++++	±
7	46	Diabetes	102 / 71	++	0
8	15	Diabetes	104 / 69	++	0
9	50	Chronic arthritis, arteriosclerosis	104 / 70	++	0
10	32	Subacute nephritis	104 / 84	++	0
11	68	Paralysis agitans, cystitis	108 / 54	++	0
12	22	? Chronic nephritis	108 / 68	++	0
13	55	Chronic nephritis	108 / 72	++	0
14	41	Diabetes	108 / 82	+++	0
15	47	Epilepsy	108 / 86	++	0
16	60	Diabetes	110 / 70	+++	±
17	65	Cancer of intestine	110 / 70	+++++	0
18	35	Diabetes	110 / 71	+++	0
19	63	Bronchial asthma, emphysema, myocarditis	112 / 70	+++++	+
20	77	Chronic bronchitis	115 / 60	+	0
21	82	Arteriosclerosis	120 / 60	++++	0
22	77	Chronic myocarditis, auricular fibrillation	120 / 62	++	±
23	77	Convalescence from pneumonia	120 / 70	++++	±
24	31	Acute bronchitis	120 / 84	++	±
25	74	Aortic insufficiency, chronic bronchitis	122 / 50	++++	+
26	54	Chronic nephritis	122 / 68	+++	±
27	73	Chronic myocarditis, chronic nephritis	122 / 71	++	+
28	55	Leukemia	122 / 80	+++	++
29	35	Acute arthritis	122 / 74	++	±
30	42	Asthmatic bronchitis	124 / 108	++	0
31	60	Diabetes	126 / 57	+++++	±
32	57	Syphilis	127 / 10	+++	+++ only 1 vessel
33	60	Diabetes	129 / 74	++++	++
34	60	? Cerebral hemorrhage	130 / 80	++++	±
35	69	Arteriosclerosis	130 / 80	+++++	±
36	58	Eczema of leg and ear	130 / 86	+++	+
37	49	Diabetes	130 / 80	+++	0
38	76	Chronic myocarditis	132 / 72	+++	±
39	38	Ovarian cyst, anemia	132 / 82	++	0
40	44	Cystitis and prostatitis	134 / 90	++	0
41	75	Chronic myocarditis	135 / 85	++	±
42	67	Cancer	136 / 66	+++++	+
43	58	Pulmonary tuberculosis	136 / 69	+++++	±
44	54	Tuberculosis ? old hemiplegia	138 / 40	+++++	±
45	67	Chronic myocarditis	138 / 90	++++	0
46	53	Chronic myocarditis	138 / 94	++	± 1 vessel
47	81	Chronic interstitial nephritis	140 / 60	++	±
48	72	Chronic myocarditis	140 / 65	++	±
49	64	Aortitis, aortic stenosis and regurgitation	142 / 28	++	0
50	59	Auricular fibrillation, chronic myocarditis	130 / 82	+++++	±

* In the column headed "Peripheral Vessels," + means slight sclerosis; ++, moderate sclerosis; +++, marked sclerosis; ++++, calcified, and +++++ "beaded." In the column headed "Retinal Vessels," ± means questionable sclerosis; +, slight sclerosis; ++, moderate sclerosis, and +++, marked sclerosis.

very young patients—one 13 and the other 15. Our impression had been that the typical patient in this group was much older than the average patient with hypertension. However, in Table 2, the average age was 53.6 years, only two years less than the average for the first group. The extremes were 23 and 85 years.

In the second table are fifty cases of peripheral sclerosis with systolic pressures over 145. The degree of peripheral sclerosis in this group averages somewhat less, the bulk of the cases being designated "moderate" or less. That these cases may show extensive sclerosis, however, is illustrated by the fact that eleven were classified as "marked" and five as "beaded" or "calcified." The lack of relationship between

TABLE 2.—*Sclerosis in Persons with a Systolic Pressure over 145* *

Case No.	Age	Diagnosis	Blood Pressure	Peripheral Vessels	Retinal Vessels
1	39	Chronic nephritis	160 /108	+++	+
2	86	Fractured hip	164 / 80	+++++	±
3	26	Vascular hypertension	166 / 96	+++	++
4	59	Vascular hypertension	170 /100	+±	+++++
5	63	Vascular hypertension	174 /112	+++++	++++
6	44	Chronic nephritis	178 /120	++	++++
7	63	Chronic nephritis	180 /120	++	+++
8	54	Chronic nephritis and myocarditis	184 /114	+++	++
9	60	Aortic insufficiency, syphilitic aortitis, myocarditis	186 / 78	++++	++
10	51	Diabetes mellitus	188 / 92	++	++
11	58	Hypertension, chronic myocarditis	188 /112	+++	+++
12	54	Chronic nephritis	189 /110	++	++
13	71	Hypertrophic arthritis	190 / 90	+	+++
14	52	Chronic nephritis	190 /100	++	+++
15	61	Auricular fibrillation	190 /110	++	++
16	63	Chronic nephritis, myocarditis	190 /112	+++	+++
17	68	Mitral endocarditis, hernia	190 /120	++	+++
18	48	? Chronic nephritis	190 /140	+++	+++
19	80	Tabes, necrosis of bone	192 / 80	+++	++
20	26	Chronic nephritis, myocarditis	192 /120	+++	+++
21	75	Chronic myocarditis	194 / 94	++++	+++
22	52	Vascular hypertension	194 /112	++	++
23	56	Asthma	195 /112	+	+++
24	62	Cerebral hemorrhage, old	196 /113	++	+++
25	52	Cerebral hemorrhage	198 /110	+	+++
26	23	Chronic nephritis	199 /158	++	++++
27	46	? Chronic myocarditis, ? aortitis	202 /144	++	+++
28	53	Chronic myocarditis, ? chronic nephritis	205 /105	++	+++
29	56	Vascular hypertension	208 /112	++	+++++
30	85	Chronic nephritis	210 /112	++++	++
31	57	Chronic nephritis, myocarditis	210 /116	++	+++
32	46	Chronic myocarditis	210 /130	++	+++++
33	51	Myocarditis	215 /130	++	++
34	37	Chronic nephritis	216 /124	++	++
35	48	Chronic myocarditis	216 /138	+±	++++
36	29	Chronic nephritis, myocarditis	216 /168	++ +	+++
37	43	Vascular hypertension	218 /104	++	+++
38	47	Chronic nephritis	218 /144	+++	++
39	77	Aortic insufficiency, chronic nephritis	220 / 90	+	+++
40	52	Chronic nephritis	220 /134	+++	++
41	74	Inguinal hernia	222 /108	++++	+++
42	57	Vascular hypertension, cirrhosis of liver	225 /104	+	+++
43	57	? Chronic nephritis	232 /120	+	++
44	57	Vascular hypertension	232 /130	++	+++
45	47	Chronic nephritis	234 /105	++	+++
46	45	Chronic nephritis	234 /160	+	+++++
47	43	Chronic nephritis	240 /115	++	+++
48	41	Chronic nephritis, myocarditis	242 /154	++	+++
49	58	Chronic myocarditis, arthritis	254 /110	±	+++
50	30	Chronic nephritis, myocarditis	266 /130	++	+++

* Under "Retinal Vessels," ++++ means beading and +++++ indicates vessels represented merely by white lines. Other signs have same meaning as in Table 1.

peripheral and retinal sclerosis is particularly well demonstrated in this table. The patient in Case 2 had radial vessels that were definitely calcified, and yet the retinal vessels showed only questionable pressure effects and unevenness. In contrast is Case 46 in which the radials were only slightly thickened and tortuous, while many of the retinal vessels were so sclerosed that they were represented merely by white

lines. What was said about the lack of relation between blood pressure and peripheral sclerosis is, therefore, confirmed in this group. This lack of relationship extends also to the retinal sclerosis. The last column shows clearly that there is a marked association between hypertension and retinal sclerosis. Closer scrutiny will show that the height of the pressure is independent of the degree of retinal sclerosis. There is a tendency for high diastolic pressures to be associated with the higher degrees of retinal sclerosis, but this is only a tendency. Several cases with high diastolic pressures show only moderate pressure effects and unevenness in these vessels. Furthermore, many of the cases of marked sclerosis are in patients with a relatively low systolic or diastolic pressure. We can hardly expect such a relationship. The blood pressure is so variable and fluctuates so markedly from moment to moment that it is inconceivable that it could be entirely dependent on a factor so fixed as arteriosclerosis of the small blood vessels. The

TABLE 3.—*Degree of Sclerosis of Retinal Vessels in Hypertensive and Nonhypertensive Cases*

	Hypertensive Group, Percentage	Nonhypertensive Group, Percentage
Normal arteries	0	44
Questionable sclerosis	2	38
Slight sclerosis	2	8
Moderate sclerosis	28	8
Marked sclerosis	52	2
Beaded sclerosis	8	0
"White line"	8	0
	100	100

vasoconstrictor and vasodilator elements as well as the heart are factors which always must be considered.

Although the relationship between the degree of retinal sclerosis and the blood pressure is not a quantitative one, there is no question about a qualitative relationship (Table 3). To us the proof seems absolute.

The contrast between the two groups is indeed extraordinary: Whereas, in the hypertensive patients 68 per cent. showed a grade of retinal sclerosis classified as "marked" or even more than that, in the other group, 82 per cent. had practically normal vessels and only one case showed "marked" sclerosis. In this patient, moreover, the marked unevenness of caliber was confined to a single vessel.

During our search for persons with low pressure and sclerosis, four cases were discovered which were extremely stimulating and confirmatory of what we have written in the foregoing on the relation between retinal sclerosis and hypertension. These cases are the first four in Table 4. They were presented to us as cases of peripheral sclerosis with normal blood pressure. Without knowing anything more

about the patients, we made an examination of the fundi, and found that two of the patients showed marked sclerosis and two moderate sclerosis. These four cases offer the strongest proof of our thesis. On obtaining the histories of the patients, we discovered that all of them had previously been hypertensive, as indicated in Table 4. We have subsequently added twelve more cases from our records which illustrate the same phenomenon. In only two were the retinal vessels normal. Such facts offer much food for thought. They suggest strongly that although hypertension occasionally occurs without evidence of sclerosis in the retinal vessels, the finding of the latter indicates the probability of a previous hypertension.

TABLE 4.—*Patients with Normal or Low Pressure Who Previously Have Had Hypertension*

Case No.	Blood Pressure	Previous Blood Pressure	Retinal Vessels
1	120 / 80	170/ 96	+++
2	134 / 65	162/ 72	++
3	144 / 72	160/ 80	++
4	147 / 85	210/100	++++
5	108 / 72	208/100	0
6	128 / 68	200/100	+
7	130 / 82	240/102	++
8	132 /112	190/158	+++
9	140 / 80	270/190	++
10	142 / 98	180/ 35	0
11	142 / 80	192/100	+
12	142 / 86	180/120	+
13	142 / 88	180/ 90	++
14	144 / 94	190/100	+
15	148 / 87	172/ 84	+
16	150 / 68	185/ 90	+++++

To us, these observations, even in a small series of 100 cases, are of special importance. First, they emphasize the great importance of examining carefully the retinal vessels instead of merely glancing at the fundi for the far less important hemorrhages and white spots. It has been shown definitely by Moore [6] that the condition of the retinal arteries is a close guide to the condition of the cerebral vessels. Consequently, they must be of considerable prognostic value. Then, too, the finding of retinal arteriosclerosis in patients with a normal or low blood pressure probably indicates, as in our sixteen cases, the existence of a previous hypertension with a subsequent myocardial weakening or loss of vascular tonus. This finding would have done much to solve the difficulty experienced by Janeway and others in deciding which arteriosclerotic patients had a low tension because of cardiac weakness and which had always had low tension. It is often of the greatest importance from the point of view of diagnosis, and particularly of prognosis, to be able to decide such a question. These facts also bring

6. Moore, F.: Quart. J. Med. **10**:29, 1916-1917.

out the great clinical difference that exists between arteriosclerosis confined to vessels of the first and second order of magnitude and those of the third.

Our results definitely establish the fact that the peripheral vessels play little or no part in hypertension. They do show, however, a definite relationship between small vessel sclerosis, indicated in the retinal arteries, and high blood pressure. Nothing was developed from these observations to prove whether hypertension comes first and sclerosis second, or vice versa. But they do get closer to the facts. Undoubtedly, many cases of essential hypertension which are said to be free from association with arteriosclerosis, in reality may have a considerable degree of sclerosis of the small blood vessels. Undoubtedly, too, there are many cases of early hypertension in which no sclerosis of the retinal vessels can be made out. We wish to call attention, however, to the findings of Cohen,[4] who noticed the absence of any apparent retinal arteriosclerosis as observed through the ophthalmoscope but the presence of retinal arteriosclerosis in the same patient when the retina was observed microscopically. He also calls attention to the fact that choroidal arteriosclerosis was present without retinal arteriosclerosis, and when both were present the former was even more marked than the latter. One other thought arises in conjunction with this work. We must assume that this disorder of small vessels is more or less general. We cannot think for an instant that hypertension is associated only with sclerosis of the retinal arteries. These are probably, therefore, a fair index of small vessels throughout the body.

OBSERVATIONS ON PULSUS PARADOXUS (WITH SPECIAL REFERENCE TO PERICARDIAL EFFUSIONS)

I. CLINICAL *

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The occasional occurrence of a marked respiratory variation in the amplitude of the pulse was first described in 1850,[1] and since that time many reports concerning its clinical significance have appeared. The opinions expressed in regard to the probable cause and significance of this phenomenon have been manifold, diverse, and often contradictory; so much so, perhaps, that modern writers seem inclined to look on the question of pulsus paradoxus as the remnant of an unfinished polemic. During the routine examination of a large number of patients coming into the hospital, we were impressed by the appearance of pulsus paradoxus in certain types of disease. Observations were therefore made on these patients; and animal experiments were devised to aid in the clinical interpretation of this interesting pulse phenomenon.

The first critical exposition of pulsus paradoxus was presented by Kussmaul [2] in 1874. His polygraphic records were not complete, but his detailed descriptions of three cases, including one previously reported by Griesinger,[3] leave no doubt concerning the precise nature of the condition which he observed. Because of the prevailing misconception of Kussmaul's work and the vague manner in which many textbooks allude to the pulse which justly bears his name, it seems appropriate to quote from his original contribution. After thoroughly describing the pathologic entity of fibrous mediastinopericarditis with thoracic adhesions, he continues:

> Clinically our affection of chronic inflammation of the pericardium and its obliteration, which is a criterion of mediastinitis, leads to a peculiar pulse phenomenon from time to time associated with unusual behavior of the neck veins. During the time that the sternum with each inspiration exerts a narrowing tug upon the ascending arota or the arch, the pulse in all the arteries becomes regularly and rhythmically smaller, while the heart movements remain constant. Thus with each inspiration, at regularly repeated intervals, the pulse becomes smaller to return again with expiration. I propose, therefore, to call this the paradoxical pulse, partly because of the peculiar disproportion between the heart activity and the arterial pulse; partly because the pulse, in spite of the seeming irregularity, in reality has become a regularly recurring waxing and waning.

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1. Williams, C. J. B.: London J. Med. **2**:164, 1850.
2. Kussmaul, A.: Berl. klin. Wchnschr. **10**:433, 445, 461, 1873.
3. Griesinger, W., quoted by Kussmaul, Footnote 2.

In the light of this excellent clinical and pathologic report, one is inclined to accept Kussmaul's use of the term "paradox" as legitimate in spite of the fact that it is frequently referred to as a "misnomer" [4] or a "poorly chosen name." [5] Such statements are not based on a fair appreciation of Kussmaul's work, and tend to discredit any clinical significance which this phenomenon may possess.

A great deal of discussion has appeared in the literature since this classical research. Clinicians and physiologists have endeavored to justify their own interpretations of the phenomenon, generally, however, with insufficient evidence to support them. Soon after Kussmaul's report, Sommerbrodt [6] claimed that the so-called paradoxical phenomenon was in reality a normal event which could be found in nearly all healthy persons during deep breathing, especially those with powerfully developed thoracic muscles. Reigel [7] observed it in a typhoid patient after severe hemorrhage, and believed that myocardial weakness played the important rôle in such cases. His main idea, however, was that the pulsus paradoxus was due to an incomplete filling of the aortic system which might result from a deep inspiration. Gaisböck's [8] observations led him to conclude that this pulse is produced by a reflex vasomotor mechanism acting through the medullary center. He supposed that a peripheral constriction occurs during inspiration causing a diminished volume of the radial artery. Falconer and McQueen,[9] Hewlett,[10] P. W. Williams,[11] Edgecombe,[12] Harris,[13] and others, reported observations on the decrease in volume in the radial arteries (usually in one only) during inspiratory movements of the thorax which have been shown to be the result of oval compression of the subclavian artery between the first rib and the clavicle. This feat is accomplished by practiced contortions of the thoracoscapular groups of muscles and is necessarily limited to the arteries beyond the constricting point. Rosenbach [14] proposed that kinking of the inferior vena cava by the contracting diaphragm would explain the inspiratory diminution in the arterial pulse wave in some cases. Traube [15] and Wenckebach [16] held that

4. Lewis, T.: J. Physiol. **37**:233, 1908.
5. Sahli, H.: Treatise on Diagnostic Methods, Ed. 4, Philadelphia, W. B. Saunders Company, p. 126.
6. Sommerbrodt, H.: Berl. klin. Wchnschr. **14**:615, 1877.
7. Riegel, F.: Deutsch. med. Wchnschr. **24**:345, 1903.
8. Gaisböck, F.: Deutsch. Arch. f. klin. Med. **110**:506, 1913.
9. Falconer, A. W., and McQueen, T. M.: Quart. J. Med. **8**:38, 1914.
10. Hewlett, A. W.: A Unilateral Paradoxical Pulse, J. A. M. A. **45**:1405 (Nov. 4) 1905.
11. Williams, P. W.: Brit. M. J. **2**:369, 1907.
12. Edgecombe, W.: Brit. M. J. **2**:890, 1920.
13. Harris, T.: Lancet **1**:1072, 1899.
14. Rosenbach, O.: Arch. f. path. Anat. u. Physiol. **105**:215, 1886.
15. Traube, L.: Berl. klin. Wchnschr. **13**:369, 1876.
16. Wenckebach, K. F.: Brit. M. J. **2**:369, 1907; Ztschr. f. klin. Med. **7**:402, 1910.

adhesions, such as are found in mediastinopericarditis with obliteration of the sac, will directly embarrass the action of the heart by virtue of the tension which they exert on it during inspiration.

The apparent relationship between the pulsus paradoxus and intrapleural pressure variations has been pointed out by Wenckebach,[16] Reichmann[17] and others. Every one is familiar with the simple experiments of Valsalva and Müller, in which respiratory efforts are made with the glottis closed. However, the effects of these experiments on pulse volume and pressure have been variously interpreted. In fact, there has been a long period of controversy among physiologists concerning the exact effect of respiration on cardiodynamics.

After reviewing the literature, one feels that Kussmaul's original position remains valid, but there is sufficient evidence to suggest that as a diagnostic factor its possibilities should be more clearly defined and extended. One of the first logical steps in this direction was undertaken by Schreiber,[18] who separated the "true" pulsus paradoxus from the "false" types. "True" pulsus paradoxus, he said, must conform to the following stipulations: (1) it must be felt in all accessible arteries; (2) it does not require a deep inspiration; (3) there must be no irregularity of the heart action. Thus he excluded the many case reports which involve compression effects on certain arteries, voluntary exaggeration of breathing, and pure sinus arrhythmias. Other observers[19] have emphasized the important distinction between the dynamic type which results from respiratory conditions, modifying the intrapleural pressure, and the mechanical variety which is produced by the tugging of mediastinothoracic synechia on some part of the cardiac structures.

The appearance of a paradoxical pulse in patients with pericarditis we have found to be of unusual significance. True, most of the controversy concerning pulsus paradoxus has centered around this pathologic condition, but curiously enough it appears that so much attention has been given to the adhesive forms that the serous types have been neglected. Our interest in the paradoxical phenomenon was first stimulated by the striking examples observed in patients with pericardial effusion.

Definition and Classification of Pulsus Paradoxus

In order to limit the discussion, we attempt to define and classify pulsus paradoxus. By a pulsus paradoxus, pulsus respiratio, or Kussmaul's pulse, we mean a rhythmical pulse which diminishes perceptibly in amplitude or is totally obliterated during inspiration in all palpable arteries. It is a periodic waxing and waning of pulse amplitude, which

17. Reichmann, E.: Ztschr. f. klin. Med. **53**:112, 1904.
18. Schreiber, J.: Arch. f. Exper. Path. u. Pharmak. **12**:168, 1880.
19. Wenckebach: Footnote 16. Semerau, M.: Deutsch. Arch. f. klin. Med. **115**:608, 1914.

from the standpoint of clinical interest must occur without conscious effort on the part of the patient to modify his breathing. This diminution in pulse amplitude is always accompanied by a fall in systolic blood pressure. We wish to lay particular emphasis on the fact that we are dealing with a practical clinical problem, and therefore we exclude all pulse phenomena which cannot be detected by the palpating finger and likewise any instances in which the subject intentionally influences the character of his respiration.

Clinical Classification of Pulsus Paradoxus

The clinical material which we have gathered on this pulse phenomenon can be best arranged, we believe, as follows: [20]

GROUP I. Abnormal conditions of the respiratory system.
- *A.* Partial tracheal or bronchial stenosis: bronchiolar spasm, laryngeal croup.
- *B.* Pathologic processes impairing lung extensibility: pneumonia, chronic emphysema.
- *C.* Involuntarily exaggerated breathing.
  - (1) Uncomplicated: acidosis.
  - (2) Associated with cardiovascular inefficiency: severe hemorrhage, myocardial failure.

GROUP II. Pathologic conditions of the pericardium.
- *A.* Mediastinopericardial adhesions.
- *B.* Pericardial effusion.
  (Paramediastinal encapsulated pleural effusion.)

Pulsus Paradoxus Associated With Abnormal Conditions of the Respiratory System [21]

It did not seem advisable to report all our cases of pulsus paradoxus in statistical fashion, but rather to cite a few examples commonly seen in the clinic and to offer an interpretation of the phenomenon in these cases.

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20. Congenital anomalies of the circulation, such as patent ductus arteriosus, have been reported as a condition producing pulsus paradoxus. Francois-Franck (quoted by Reichmann, Gaz. méd. de Paris, No. 50, 1878), among others, believed that in such conditions the waxing and waning of the pulse was due to a shunting of aortic blood into the pulmonary artery during inspiration, thereby decreasing the volume of the aortic pulse wave. This explanation may be correct, provided a free flow of blood from the aorta occurs under such conditions. Cases of this nature are seldom observed, however, and a clinical diagnosis is difficult to establish. Furthermore, a recent experience has cast some doubt on the contention that pulsus paradoxus may be produced by a patent ductus arteriosus. Two cases of aneurysm of the sinuses of Valsalva which perforated into the pulmonary artery, causing a free anastomosis between the two vessels, have been intensively studied in this clinic. Neither of these showed a paradoxical pulse. Both came to necropsy and will be reported by Dr. R. W. Scott.

21. Our animal experiments (Katz, L. N., and Gauchat, H. W.: Arch. Int. Med., this issue, p. 371, have demonstrated conclusively that the intrapleural pressure is the prime factor responsible for the pulsus paradoxus in this group.

Partial Tracheal or Bronchial Stenosis (Group 1, *A*).—Pulsus paradoxus was frequently found in patients suffering from acute asthmatic attacks. The presence of a marked increase in the negative intrapleural pressure was evident in these patients by the retraction of the intercostal spaces, the narrowing of the costal angle and the vertabraed movement of the ensisternum during inspiration. The prompt relief from this respiratory embarrassment which was secured by the administration of epinephrin resulted in a coincident disappearance of the paradoxical pulse.

Similar observations were made in cases of tracheal obstruction due to aneurysm of the transverse aorta or mediastinal tumor. We also observed a paradoxical pulse in children with diphtheria striving desperately to breathe against partial obstruction of the larynx. The dramatic relief given by intubation or tracheotomy was promptly followed by disappearance of the waxing and waning of the pulse. Gerhardt,[22] in 1895, emphasized this manifestation of the pulse as an

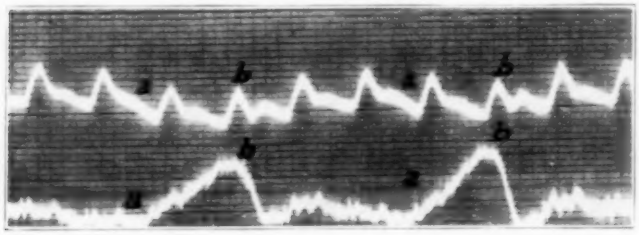

Fig. 1.—Pulsus paradoxus in a patient with chronic bronchitis and emphysema. Upper curve is an optical record of the right radial artery obtained with Wiggers' pulse recorder (Wiggers, C. J., and Baker, W. R.: Am. J. Physiol. **59**:454, 1922) and segment capsules. Lower curve of respiration was taken simultaneously by means of a cup tambour fastened over the epigastric region by an elastic band—upstroke inspiration, downstroke expiration. Vertical lines denote 0.1 of a second, horizontal lines 1 mm. apart; *a*, beginning of inspiration; *b*, beginning of expiration.

indication of the onset of the stage of asphyxia in cases of laryngeal croup.

Pathologic Processes Impairing Lung Extensibility (Group 1, *B*).—We have found frequent instances of the paradoxical pulse associated with diseases which involve the parenchyma of the lung. A particularly striking example (Fig. 1) was seen in a child with acute bronchopneumonia following measles. In this case, diffuse infiltration and consequent inexpansibility of the bases of the lungs made it necessary for the patient to accomplish respiration entirely by the use of the thoracic

22. Gerhardt, C.: Berl. klin. Wchnschr. **34**:4, 1897.

cage. The extraordinary effort required to ventilate a lung whose elasticity was distinctly reduced demanded an increase in the depth and the velocity of inspiration.

Pulsus paradoxus was found in all varieties of pneumonic infiltration. The fact that many cases of pneumonia do not exhibit the phenomenon suggests that the volume and elasticity of the unaffected lung areas may suffice to carry on respiration without causing an undue increase in the intrapleural pressure values. Although the respiratory rates which accompany pneumonic affections are usually rapid, this does not necessarily imply that the pleural pressure variations are appreciably increased. There is no practical clinical method of measuring intrapleural pressure, but careful attention to the patient's mechanism of breathing usually permits a reasonably accurate estimation.

While making observations in a large number of cases with well advanced pulmonary tuberculosis, we were somewhat surprised to find

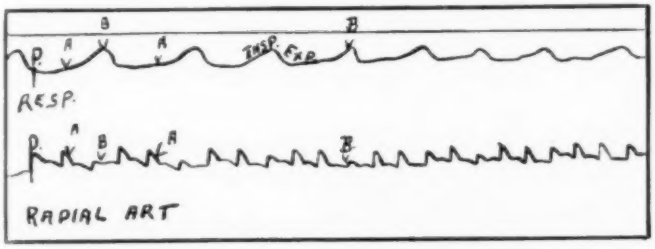

Fig. 2.—Pulsus paradoxus in a patient with diffuse bronchopneumonia. Record obtained as in Figure 1, except that a Mackenzie polygraph was used in place of the optical capsule. *P* denotes comparable points. Upper curve is respiration, upstroke inspiration.

that these patients did not have a paradoxical pulse. This may be due to the fact that the majority of tuberculous patients in spite of extensive parenchymal involvement do not, as a rule, have an increased *depth* of breathing. The slow process of infiltration and cicatrization probably allows ample time for the unaffected lung areas to assume the ventilatory function without an increase in intrapleural pressure variations.

Several patients with chronic emphysema were observed in periods of acute pulmonary decompensation at which time the pulsus paradoxus was quite marked (Fig. 2). On recovering from these attacks of severe bronchitis and the establishment of a fairly normal type of breathing, the paradoxical pulse disappeared entirely. It is not surprising that our cases of pulmonary emphysema exhibited the most marked examples of pulsus paradoxus seen under Group 1, when one

considers the nature of this pathologic condition. There is probably no chronic process which should be more effective in modifying intrapleural pressure values than chronic bronchitis and emphysema, for here we may have the combined effects of bronchiolar stenosis, rigidity of the lung, and an inefficient action of the diaphragm. In fact, the handicap offered to pulmonary expansion by these factors probably causes more marked changes in intrapleural pressure than might be suspected from examination of the patient.

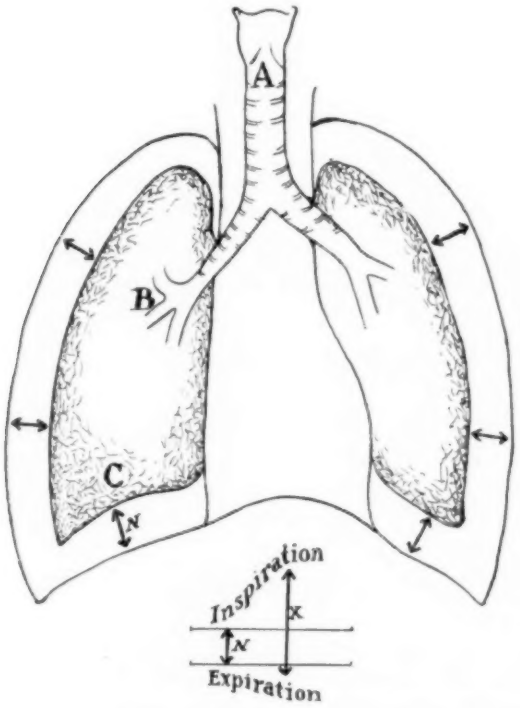

Fig. 3.—Diagrammatic scheme of the respiratory mechanism. Arrows placed in the pleural spaces represent the variation in pressure during a normal respiration. *N* represents the normal variation; *X*, an exaggerated value which is sufficient to produce a pulsus paradoxus. The value *X* may be produced by increasing the excursion of the thorax by stenosis of the trachea or larynx indicated by *A*, by bronchial stenosis (*B*) or pulmonary infiltration (*C*).

Involuntarily Exaggerated Breathing (Group 1, *C*).—In the routine examination of patients suffering from renal or diabetic acidosis we frequently observed a pulsus paradoxus. We found some patients with renal acidosis, however, who had a considerable increase in the

tidal air, but because the *velocity* (that is, the gradient of the variations in intrapleural pressure) was not increased (both inspiration and expiration being prolonged) there was no palpable variation in the pulse wave.

Respiratory and circulatory conditions occasionally combine their effects to produce a pulsus paradoxus. For example, we found a paradoxical pulse in patients under anesthesia, who had lost much blood. It was also commonly present in cases of surgical shock. Moribund patients in the stage of cardiovascular collapse frequently exhibited a pulsus paradoxus.

Comment.—We have indicated in the foregoing presentation that certain well known types of respiratory disease are frequently associated with a pulsus paradoxus. The one factor common to all these conditions is an abnormal variation in intrapleural pressure. The cause of this increase may be due to stenosis of the air passages or involvement of the pulmonary parenchyma, as pointed out in the foregoing discussion and diagrammatically represented by A, B and C in Figure 3. We have denoted the normal intrapleural pressure variation in this figure by "N," and we may assume on the basis of animal experiments given in another report that whenever this is increased to the hypothetical value "X," we may expect a pulsus paradoxus to result, regardless of the exact physical defect in the respiratory mechanism. In certain cases, marked circulatory inefficiency may play the leading rôle in the production of a paradoxical pulse.

The precise manner in which the variations in intrapleural pressure manifest themselves in the peripheral pulse, we shall leave for discussion in the report of our animal experiments. For practical purposes, it is sufficient to know that the presence of an increased intrapleural pressure variation may adequately explain the clinical production of pulsus paradoxus.[23]

It follows, therefore, that in order to offer a correct interpretation of the paradoxical pulse phenomenon as it occurs in respiratory diseases, certain signs must be looked for: Is respiration thoracic or abdominal? Do accessory muscles participate in the respiratory act? Is there retraction of the intercostal spaces? What are the evidences of excursion and activation of the diaphragm? Is the velocity of inspiration and expiration increased? Obviously, it is only by such a careful analysis of the mechanism of breathing that one can make a reasonable clinical estimate of the intrapleural pressure variation at the bedside.

23. The phenomena of cardiorespiratory interference waves recently reported by Gesell and his associates may, as they suggest, be explained on a similar basis. (Trotter, R. T.; Edson, P., and Gesell, R.: Am. J. Physiol. **60**:500, 1922).

Pulsus Paradoxus Associated With Pathologic Conditions of the Pericardium

We wish to present several detailed case reports of pericarditis. These were selected from our series because they include the various clinical forms, and moreover because they illustrate clearly the relation of pulsus paradoxus to pericardial pathology.

Mediastinopericardial Adhesions (Group II, *A*)

Case 1.—*History.*—J. S., white, a carpenter, aged 28, admitted to the hospital on Aug. 28, 1922, with a diagnosis of chronic fibrous mediastinopericarditis, became ill six months prior to admission, with shortness of breath, pain in the chest, cough, and an attack of hemoptysis which sent him to a hospital. His condition remained about the same, and after two weeks he returned home, where he had been gradually declining up to the time of his admission.

Physical Examination.—The patient was a well developed, undernourished man, propped up in bed in a comfortable attitude. An irritating cough, pain beneath the lower end of the sternum, and shortness of breath on exertion were his chief complaints. There was some edema of the dependent parts and the face. Respiration was increased in rate (26 per minute) and was predominantly thoracic in type, with impaired undulatory movement of the upper right ribs. In spite of these variations from the normal, the patient's breathing efforts were quiet and regular. The pulse was small and monocrotic in type, with a palpable waxing and waning during tranquil breathing. Blood pressure was: systolic, 120; diastolic, 80. The jugular bulb was not distended and exhibited a normal pulsation. A feeble apical impulse was perceptible in the anterior axillary line in the fifth intercostal space, and a systolic impulse and diastolic impact were felt over the area of the second and third left intercostal spaces bordering on the sternum. The percussion boundary of the heart extended to the left anterior axillary line in the fifth interspace. The right boundary of cardiac dulness formed an obtuse angle with hepatic dulness at a level with the fourth rib 4 cm. from the sternum. Auscultation of the cardiac area revealed distinct sounds at the base and apex. Reduplication of the second sound, which was only occasionally present over the base of the heart, was the only variation from normal. The liver margin was 3 cm. below the right costal border, firm and not tender. The spleen was not enlarged.

Roentgen-Ray Examination.—A large, ill-defined, pyramidal heart shadow was found encroaching on the lung areas at the bases. No pulsation was seen under the screen. Both costophrenic sinuses were cloudy. Excursion of the diaphragm was limited. Surrounding lung areas were "hazy" in character, except the right apex, which had a moderately dense cloudiness. The most unusual feature of the plate was the "shaggy" and indistinct margin of the cardiac area, which fused with the pulmonary shadows, making it difficult to determine its exact outline.

Subsequent Course.—The diagnosis of chronic mediastinopericarditis was made, with the suspicion that there might be some effusion into the sac. However, this was early excluded by ineffectual attempts to remove fluid by tapping at these points. To the right of the sternum in the fourth interspace, the trochar lodged in the auricle, and venous blood was obtained. In the left fifth interspace, the needle "grated" against the ventricular musculature. A puncture was made by inserting the trochar underneath the tip of the xiphoid cartilage through the subcardial diaphragm. By this means, 2 ounces (60 c.c.) of serosanguineous fluid were aspirated, presumably from the pericardial sac.

Sept. 11, 1922: The patient's general condition improved after a course of digitalis therapy. He was up in wheel chair. Pulsus paradoxus was observed in the erect and prone positions.

September 19: There were signs of fluid at the right lung base and 800 c.c. of clear serous effusion were removed, the specific gravity of which was 1.016. Pulsus paradoxus was still present.

September 29: Thoracentesis of the right pleural cavity (1,200 c.c.) was performed. The pulse was unchanged.

October 19: The patient's general condition was worse. There was fluid in both pleural cavities and the abdominal cavity. Abdominal paracentesis (2,500 c.c. of bloody serous exudate) was performed.

October 26: There was great difficulty in swallowing. Cyanotic, generalized edema and dyspnea were present.

On October 29 the patient died.

Synopsis of Postmortem Examination.—The heart and pericardium were universally adherent and firmly attached to the sternum, weighing together 630 gm. The pericardium was greatly thickened, particularly over the region of the coronary sulcus, at which place it was 10 mm. thick. At the apex and over the auricles the average thickness was 4 mm. The posterior portions of the pericardial membrane consisted of a layer of caseous material, and caseous tubercles were found on the anterior surface of the heart. Both lungs were everywhere adherent to the chest wall and mediastinal structures. Costophrenic sinuses and the subcardial diaphragm were covered with thick fibrous and caseous exudate. There were found also: miliary tuberculosis of the spleen, peritoneum, liver and omentum; chronic vegetative mitral valvulitis; tuberculous ulceration of the cecum; chronic passive congestion of the viscera and general anasarca.

Comment.—This clinical picture as well as the postmortem findings bears a striking resemblance to Kussmaul's [2] cases. We were unable to find any particular relation of the mediastinal adhesions to the arch of the aorta such as Kussmaul described, and thus could not confirm his contention that the pulsus paradoxus results from a kinking of the aorta by the cicatricial bands encircling it.

In another case in this group an inspiratory distention of the neck veins was observed, a phenomenon which Kussmaul also pointed out, and which he properly attributed to the mediasinal synechia.

PERICARDIAL EFFUSION (Group II, *B*)

CASE 2.—*History.*—J. S., colored, a mill worker, aged 23, was admitted to the hospital on July 31, 1920, with a diagnosis of chronic tuberculous pericarditis with effusion and tuberculous peritonitis and pleurisy with effusion. The patient had been ill for the past three months with cough, pain over the right hypochondrium, and increasing shortness of breath, all of which began with a "cold" contracted while working at a hot furnace. He had always been well until the onset of this illness.

Physical Examination.—The patient was sitting comfortably in bed, with no particular signs of illness. His breathing was slightly increased in rate (24 a minute), quiet and regular, and predominantly thoracic. The pulse showed a palpable waxing and waning with respiration in all accessible arteries. Blood pressure during expiration was: systolic, 118; diastolic, 85. The pulse rate was 90. The neck veins were somewhat distended but with normal pulsations. The tension within the jugular bulb decreased during inspiration. The temperature was 38.4 C. (101.2 F.), but the patient did not feel feverish. Chest examination revealed a large flat area of cardiac dulness extending as far as the midaxillary line on the left, and 3 cm. to the right of the sternum, where it merged with the dulness of a pleural effusion which extended up to the level of the third intercostal space anteriorly and the fifth rib in the postaxillary line. The precordial

area was flat to percussion, as much as at Louis' angle as over the lower segment of the sternum. No visible or palpable cardiac impulses were present. The heart sounds were faintly audible, and no murmurs were heard. The left lung base posteriorly had a tympanitic percussion note. The inferior border of the liver was 2 cm. above the umbilicus, with its edge rotated downward, so that it could be palpated only with difficulty.

Roentgen-Ray Examination.—An immense pyriform cardiac shadow, which did not pulsate, was observed under the fluoroscopic screen. A fluid shadow was present in the right pleural cavity, and there was a faint cloudiness over both lung areas.

Subsequent Course.—The patient remained in the hospital for one year prior to his death. He began to decline about a month after admission, on account of a dissemination of the tuberculous infection, which gradually invaded the lungs, pleura and peritoneum. The serous cavities were tapped on numerous occasions to relieve the embarrassed respiration. Six weeks before he died, a total of 7,000 c.c. of serosanguineous fluid were withdrawn in one day; 5,550 c.c. from the abdominal cavity, 1,000 c.c. from the left pleural cavity and 450 c.c. from the pericardial sac. A guinea-pig inoculated with the pericardial fluid died of tuberculosis.

This case was repeatedly used for the demonstration of pulsus paradoxus to junior medical students, and the disappearance or abatement of this phenomenon after tapping was demonstrated by the house physicians, who performed pericardial paracentesis on six occasions. Twelve hundred cubic centimeters was the largest amount removed from the precardial sac at any one time. During the last few months, the patient suffered from circulatory stasis and dyspnea. The pulse became small and rapid, so that the paradoxical effect was not a prominent feature. He died on June 25, 1921.

Synopsis of Postmortem Examination.—The pericardial sac was considerably enlarged, greatly thickened (6 mm.), and contained about a pint of clear serous fluid. The posterior portion of the sac was adherent to the heart, and the epicardium over the anterior surface was covered by a layer of caseous material 2 mm. thick. All of the mediastinal structures, especially the great vessels, were so densely adherent that it was necessary to remove them en masse.

The heart was small (not weighed), and had the characteristic appearance of brown atrophy. The endocardium, heart valves and aorta were uninvolved. There was found also serofibrinous pleuritis with bilateral sacculated effusions, discrete pulmonary tuberculosis—both apexes, atelectasis of the lower lobe of the left lung, caseous tuberculosis of the thoracic and abdominal lymph nodes, serofibrinous peritonitis with ascites (4 liters), chronic passive congestion of the viscera, perilobular cirrhosis of the liver and general anasarca.

CASE 3.—*History.*—M. Z., a white man, a laborer, aged 60, was admitted to the hospital on Nov. 20, 1919, with a diagnosis of tuberculous pericarditis with effusion. The patient said that his trouble began three weeks before admission with cough, fever and chilliness, and pain over the lower portion of the sternum. The irritating, unproductive cough did not allow him to sleep, and during the past few days aphonia and dysphagia developed. Previously he had always been well and he was accustomed to hard work.

Physical Examination.—The patient, a well nourished man, about 60 years of age, was reclining comfortably in bed. His respiration was 26; pulse rate, 96; temperature, 37 C. (93.6 F.). His cheeks, lips and ear lobes had a peculiar dusky hue, which has been aptly described as a peach-skin complexion. There was slight supramalleolar edema. The rapid, small volume pulse manifested a striking waxing and waning, being almost entirely obliterated during his tranquil inspiratory efforts. The jugular bulb became distended when the patient assumed the recumbent position. Examination of the thorax revealed a pyriform area of precordial dulness, moderate emphysema of the lungs, and moisture at both

lung bases. On auscultation over the central region of the sternum a soft to and fro friction rub was heard. The liver was displaced downward, which caused a prominence of the epigastrium.

Roentgen-Ray Examination.—This examination substantiated the clinical impression of a large pericardial effusion encroaching on both lung areas. A faint cloudiness in the right apex was suggestive of a thickened pleura.

Subsequent Course.—Because of the rather abrupt onset and the patient's good condition, it was thought at first that he suffered from an acute infection of the pericardium. The subsequent course, however, disproved the tentative diagnosis. On the third day after his admission, paracentesis of the pericardium was performed, and 500 c.c. of clear, serous effusion were withdrawn the specific gravity of which was 1.015. Fluid was still flowing from the needle, but it was thought advisable not to remove more at this time. Observations were made on the pulse, respiration and vital capacity, and it was found that these were not materially altered by the paracentesis, except for a decided lessening of the respiratory variation in the size of the pulse.

This excellent demonstration of the effect of a pericardial effusion on the pulse was repeated no less than thirteen times during a period of several months, amounts varying from 200 c.c. to 1,000 c.c. being withdrawn on each occasion. The paradoxical nature of the pulse never completely disappeared, but whenever the aspiration amounted to 500 c.c. or more, the many house physicians and students who usually witnessed the procedure noted a decided lessening in the waxing and waning of the pulse. The patient experienced considerable subjective respiratory relief, and frequently insisted that he should be tapped. Curiously enough, his heart always maintained a consistently rapid rate (from 94 to 116) regardless of the fluid content of the pericardial sac. His general condition permitted him to walk about the hospital during the day, and he enjoyed a tolerably good physical condition for one year.

During the last four months of his illness, the patient showed a rapid decline due to tuberculous invasion of the peritoneum and colon. The pericardial condition remained about the same up to the time of his death, March 8, 1921.

Synopsis of Postmortem Examination.—The pericardial sac was dilated, thickened and fibrosed. It contained 500 c.c. of bloody serous exudate, but was apparently capable of holding about a liter when filled. The heart was fairly free in the sac, and the epicardium contained small tubercles and adherent fibrinous tags. There was little caseation about the mediastinum, the extensive pericardial and pleural process being mostly fibrinous in character. The heart, with its thin layer of fibrinous exudate, weighed 325 gm. All chambers were dilated, and the myocardium was the seat of fatty degeneration. The endocardium was uninvolved, except for sclerotic thickening of the aorta and mitral valve leaflets. There was moderate senile sclerosis of the aorta. There was found also: serofibrinous peritonitis, tuberculous ulceration of the intestines and colon, acute peritonitis due to perforated ulcer of the ileum and chronic passive congestion of all viscera.

Comment.—We were privileged to observe these two similar cases throughout the entire period of illness. Frequent tapping of the pericardium demonstrated the intimate relationship existing between a distended pericardial sac and pulsus paradoxus. Necropsy examinations furnished conclusive evidence of the exact nature of the pathologic processes. The amount of fluid in these cases was found to be considerably less than the quantity actually removed from the sac during the earlier part of the patients' illness. The recognition of this fact suggests that many case reports of pulsus paradoxus attributed to the synechia found

at necropsy are open to criticism because the quantity of fluid present during the course of the disease cannot be correctly judged from the necropsy examination alone.

CASE 4.—*History.*—E. B., a colored man, a laborer, aged 28, was admitted to the hospital on Dec. 7, 1921, with a diagnosis of chronic tuberculous pericarditis with effusion and chronic tuberculous pleurisy with effusion. The patient walked into the hospital complaining of slight shortness of breath on exertion, a sensation of heaviness in the epigastrium, night sweats and general malaise. He attributed his condition to a "bad cold" beginning one month previously with "pleurisy pains" and a cough which still persisted. The patient had always been well and accustomed to hard work.

Physical Examination.—The patient, a tall, stalwart negro, sat comfortably on the edge of his bed. The first thing that impressed those who examined him was the remarkable waxing and waning of the pulse, whereas his breathing would have passed as natural except for a slight increase in rate. The jugular veins were distended and pulsating slightly. Chest examination revealed an extensive area of cardiac dulness, with absence of pulsation, and faintly audible heart sounds. The right side of the chest was flat to percussion below the fifth rib in the midaxillary line. The liver was rotated downward.

TABLE 1.—*Observations Made During Withdrawal of Pericardial Fluid (Case 4)*

Time	Quantity Withdrawn in C.c.	Mean Pericardial Pressure in Millimeters of Serous Effusion (Specific Gravity 1.025)	Remarks
10:05 a. m.	Anastomosis with manometer made	90 mm.	Pulsus paradoxus palpable in all arteries*
10:10	100	80 mm.	Patient perspiring*
10:15	30 (Total 130 c.c.)	70 mm.	No effect on pulse*
10:20	70 (Total 200 c.c.)	58 mm.	Pulsus paradoxus still palpable
10:25	110 (Total 310 c.c.)	45 mm.	Pulsus paradoxus decreased
10:40	130 (Total 440 c.c.)	30 mm.	Pulsus paradoxus cannot be palpated*
10:55	275 (Total 735 c.c.)	10 mm.	Venous pulsation noticed in jugulars
11:10	50 (Total 785 c.c.)	0	General condition good*

Patient returned to ward, and rested better than usual during the night.
* Optical records were made at these points.

Roentgen-Ray Examination.—This examination corroborated the presence of pericardial and pleural effusions.

Paracentesis of the Pericardium.—An ordinary long lumbar puncture needle, containing a tight fitting stilette, was inserted into the pericardium at a point 3 cm. to the left of the sternum in the fifth interspace. A single calibrated glass tube of 4 mm. bore was used as a manometer. A glass T-tube was interposed in the rubber tubing connecting the hilt of the needle to the manometer, and from this point the fluid was aspirated with a 200 c.c. glass syringe. Pinch cocks were used to keep the systems alternately closed off during aspiration and reading of the manometer. The heart motion could be felt against the shaft of the needle, and the point was presumably in the lowest portion of the pericardial sac near the diaphragm.

Table 1 gives the results of the operation described above, and in Table 2 we have noted the important physical factors which were observed during this procedure. The tables were made at the time of the operation, and the data

are self-explanatory. The disappearance of the paradoxical pulse on removing the fluid is of particular significance. The optical records taken at the designated intervals confirmed the impression of three observers who attended to palpation of the pulse. The paradoxical character of the pulse reappeared the next day, but not to the degree previously noted.

The patient stayed in the hospital a few weeks longer, and his general condition improved slightly. He was readmitted on Feb. 2, 1922, because of shortness of breath on exertion and a "heavy feeling in the right chest." A pulsus paradoxus was present. Thoracentesis of a large pleural effusion gave considerable subjective relief, but had no influence on the pulse. Table 3 gives the data on this procedure. A few days later his pericardium was tapped in two places

TABLE 2.—*Observations Before and After Paracentesis of the Pericardial Sac (Case 4)*

Observation	Before Paracentesis	Immediately After Removal of 785 C.c.
Pericardial pressure	94-90 mm.	0 mm.
Pulse rate	110	114
Pulse amplitude	Moderately small	Increased
Arterial pressure	140-100 mm.	132-98 mm.
Lateral boundaries of cardiac dulness	Left midaxillary line	2 cm. outside midclavicular line
Lower margin of liver	4 cm. below right costal margin	Edge felt at level of right costal margin
Respiratory rate	34	32
Type of breathing	Predominantly thoracic	Thoracic-abdominal
Vital capacity	1,740 c.c.	1,825 c.c.
Neck veins	Distended with slight visible pulsation	Pulsating with decreased distention
General condition	Fairly good	Breathing feels much easier with disappearance of the "heavy" sensation in epigastrium

TABLE 3.—*Effect of Thoracentesis of Right Pleural Cavity on Pulsus Paradoxus (Case 4); 1,654 C.c. Clear Serous Effusion Withdrawn (Sp. Gr. 1.016)**

Observation	Before Thoracentesis	After Withdrawal of Fluid
Fluid pressure	110-107 mm.	5-2 mm.
Fluoroscopy	Density in lower half of right lung	Lung practically clear; large pear-shaped cardiac shadow
Pulse rate	114	112
Respiratory rate	36	34
Blood pressure	145-110 mm.	145-110 mm.
Vital capacity (sitting)	1,700 c.c.	1,850 c.c.
Pulsus paradoxus	Readily palpable	Unchanged

* Patient sitting up in bed in a comfortable position; needle inserted at right tenth intercostal space in midaxillary line; fluid slowly aspirated into a 100 c.c. syringe; following the thoracentesis breathing felt easier to the patient, and there was evidence of excursion of the right diaphragm.

and no fluid obtained except venous blood from the auricle.[24] During the remainder of his stay in the hospital, his right pleural cavity was tapped four times, and an average of 1,100 c.c. of serous effusion removed each time, but without effect on the pulsus paradoxus. He requested his discharge on March 10, 1922.

CASE 5.—*History.*—G. H., a colored man, a laborer, aged 31, was admitted to the hospital on Aug. 22, 1922, with a diagnosis of chronic tuberculous peri-

24. We were somewhat at a loss to explain our inability to obtain fluid from the pericardium at this time in spite of the indications of its presence by physical signs and roentgen-ray findings. Perhaps the two months that had intervened since the last successful paracentesis allowed the heart to become adherent anteriorly, thus obstructing access to a posterior collection of fluid.

carditis with massive pericardial effusion. This patient had had influenza in 1917, with prompt recovery. In 1920, he had had a chancre which he had treated himself. He considered his general health very good until two months before admission, when he began having pain in the abdomen, dizziness, night sweats and shortness of breath on exertion. He kept at his work until the day preceding his admission, when a severe spell of breathlessness forced him to give up.

Physical Examination.—The patient was a large, muscular type of negro, sitting in bed, in no apparent discomfort. His temperature was 37.4 C. (99.3 F.). Pulsus paradoxus was striking regardless of whether the patient was in a prone or erect position. When attempts were made by this patient to adapt his respiration as nearly as possible to the thoracic or abdominal type, the paradoxical character of the pulse remained unmodified. The jugular bulb was moderately distended and refilled from the cardiac end when obliterated by stroking with the finger.

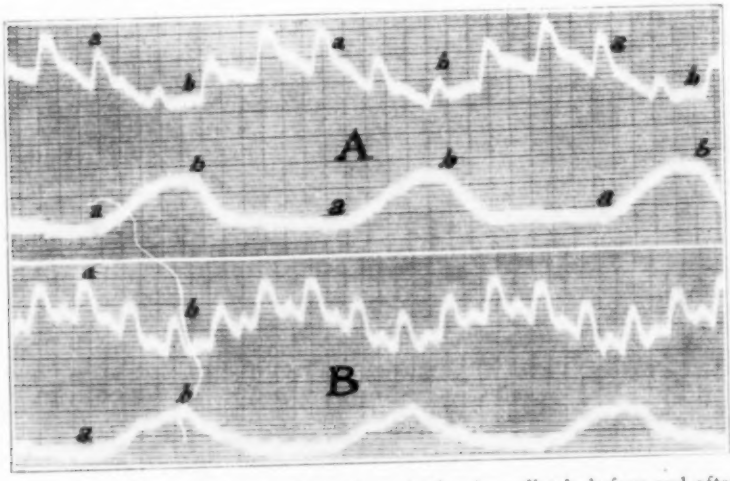

Fig. 4.—Optical record of pulse and respiration immediately before and after removal of 950 c.c. of fluid from the pericardial sac (Case 5). Record obtained as in Figure 1. Vertical lines 0.2 of a second apart. *A* shows pulsus paradoxus before removal of fluid and *B* its complete disappearance following paracentesis of the pericardium. Shifting base line of the pulse curve is an artefact caused by movements of the wrist.

Percussion of the thorax revealed a large flat cardiac area extending to the midaxillary line on the left, and on the right to the midclavicular line, forming an obtuse angle with the liver dulness. The excursion of the upper four ribs was accentuated but symmetrical on the two sides, and there was inspiratory narrowing of the costal angle. The percussion note of the left lung base was impaired posteriorly, with fine crepitant râles on auscultation of this area. The lower margin of the liver was percussed but not palpated 2 cm. above the umbilicus.

Roentgen-Ray Examination.—An immense pyriform cardiac shadow which did not pulsate was observed under the screen. The small lung areas shown in the plate were fairly clear. The findings were quite characteristic of a large pericardial effusion.

Paracentesis of the Pericardium.—On Aug. 28, 1922, the pericardium was tapped according to the technic described in Case 4. The observations made during this procedure are shown in Table 4. The disappearance of the pulsus paradoxus was the most striking feature observed, as shown in the optical tracings of the pulse (Fig. 4).

The pericardial sac promptly refilled, and the patient was tapped again on several occasions. The observations noted at the first tapping were confirmed each time. The patient left the hospital four weeks after admission at his own request.

Comment.—The therapeutic experiments in these two cases demonstrate clearly that the pericardial effusion was the direct cause of the paradoxical phenomenon, since pulse rate, blood pressure, respiration and all other factors of importance remained practically unchanged, while the paradoxical character of the pulse disappeared. The observations made on thoracentesis in Case 4 indicated that the presence of a large free pleural effusion had no effect on this pulse phenomenon.

TABLE 4.—*Effect of Paracentesis of Pericardial Sac on Pulsus Paradoxus (Case 5); 950 C.c. Serosanguineous Fluid Removed (Sp. Gr. 1.022)*

Observation	Before Paracentesis	Immediately After Paracentesis
Pulsus paradoxus	Marked*	Absent*
Pericardial pressure	78-74 mm.	7-4 mm.
Pulse rate	100	110
Pulse volume	Moderate	Increased
Arterial pressure	Expiration 130-88 mm.. Inspiration 110-88 mm.	Not recorded
Fluoroscopy	Immense pear-shaped heart shadow	Much diminished in size
Lower liver margin	4 fingers below right costal margin	2 fingers higher
Respiratory rate	24	24
Vital capacity	1,450 c.c	Not recorded
Neck veins	Inspiratory distention	Less distention, slight pulsation
General condition	Fairly good	Breathing easier

* See Figure 4 for optical records of respiration and pulse.

Analysis of the pulse tracings in these cases shows that they all have the same time relationship to respiration. The change in pulse amplitude always takes place in the first or second beat after the onset of the respiratory phase.[25]

CASE 6.—*History.*—N. E., a white man, a clerk, aged 36, was admitted to the hospital on Oct. 27, 1922, with a diagnosis of acute septicemia and acute purulent pericarditis. About three weeks before admission, an abscess had formed on the axillary surface of the right arm. The patient became quite sick with fever and chills, and the abscess was incised. The local condition improved, but his general condition became rapidly worse.

25. This applies to all cases of pulsus paradoxus (both Groups I and II) which we have studied. We mention it here to dispel any ideas concerning a possible temporal difference in the paradoxical pulse curves found under different clinical conditions. However, we have noted a variability in the degree of change in pulse amplitude. As a rule, the cases in Group II showed a more striking fluctuation in the size of the pulse than those in Group I.

Physical Examination.—The patient was a well developed man presenting the picture of a severe acute infection and who was at times irrational. The incised abscess was entirely healed. The temperature was 40.2 C. (104.3 F.). His respiration was 30. The pulse rate was 134. The leukocyte count was 16,000. Blood culture showed *Staphylococcus aureus.* The impression was that the patient was suffering from an acute septicemia, which probably originated from the abscess in the right arm.

Subsequent Course.—Nov. 4, 1922: The patient developed a pulsus paradoxus, and an audible friction rub was heard over the fourth rib to the left of the sternum. Swallowing became so painful that fluids were given by hypodermoclysis. There was cardiac dulness 2 cm. to the left of the midclavicular line and at the right margin of the sternum.

November 7: Pericardiocentesis was performed in the left fourth intercostal space 2 cm. from the sternum. Fifty cubic centimeters of turbid straw colored fluid containing pus cells and numerous gram-positive cocci were withdrawn. *Staphylococcus aureus* was obtained from culture of the pericardial fluid.

November 9: There was marked pulsus paradoxus. Two hundred and fifty cubic centimeters of purulent fluid were withdrawn from the pericardial sac, without any effect on the pulse. The condition of the patient made it inadvisable to remove more fluid. The blood pressure was: systolic, 118; diastolic, 80 before and after removal of fluid. Signs of infiltration were developing at the base of the left lung.

November 12: The patient died.

Synopsis of Postmortem Examination.—The pericardial sac was distended and contained 850 c.c. of seropurulent fluid. No adhesions were present. The parietal pericardium was of normal thickness, and the epicardium was covered by a thin layer of fibrinopurulent exudate. There was found also: acute seropurulent pleuritis, left, 500 c.c.; multiple abscesses of lungs; focal, purulent nephritis and myocarditis; acute splenic hyperplasia and duodenal ulcer.

Comment.—This case illustrates the diagnostic importance of pulsus paradoxus associated with acute infectious conditions. Without the proper interpretation of the patient's pulse, the early discovery of the purulent effusion probably would not have been made. Paracentesis was of little benefit here, because of the multiple foci of infection throughout the body. However, similar cases have been reported cured by surgical drainage of the pericardial sac, and it is interesting to note that such a case was presented before the Royal Medical and Chirurgical Society in 1883.[26] In this case particular emphasis was placed on the fact that free drainage of 2 liters of pus from the pericardium at once relieved the urgent symptoms, and the pulsus paradoxus, which had been striking, immediately disappeared.

PARAMEDIASTINAL PLEURAL EFFUSION

CASE 7.—*History.*—R. B., a colored man, a laborer, aged 36, was admitted to the hospital on Sept. 12, 1921, with a diagnosis of universal mediastinopericarditis with obliteration of sac (necropsy); chronic fibrous pleuritis with encapsulated left pleural effusion and pulmonary tuberculosis. The patient was sent to the hospital for active pulmonary tuberculosis. During the past few months he had noticed increasing shortness of breath and edema of the legs. He suffered in addition from constant severe pain across the lower portion of the sternum.

26. West, S.: Brit. M. J. **1**:814, 1883.

Physicial Examination.—The patient was a medium sized, undernourished colored man in an orthopneic position. His temperature was 38.2 C. (100.7 F.). Breathing was accomplished almost entirely with the upper portion of the thoracic cage. There was a vertebraed retraction of the ensisternum. Examination of the lungs revealed the lower margins of the bases to be higher than normal, with a total absence of tidal excursion. There was evidence of an active tuberculous infiltration at the right apex.

The cardiac area of dulness extended 1 cm. beyond the anterior axillary line on the left and 2 cm. beyond the right margin of the sternum, where it formed a right angle with hepatic dulness. The apical impulse was not palpable, but the impulse and impact over the base of the heart was rather pronounced. The heart sounds were distant at the apex without friction rubs or murmurs. The pulse was rapid (110), of small volume, monocrotic in type, and exhibited a decided respiratory waxing and waning. The jugular bulb was notably distended, with slight pulsation. The enlarged liver made a definite epigastric prominence and was tender to palpation. There was dependent edema of the extremities and back.

Roentgen-Ray Examination.—A large rounded cardiac shadow was noted, which almost filled the entire left side of the chest and extended slightly beyond the right margin of the sternum. It formed approximately a right angle with the right diaphragm. The costophrenic sinuses were clouded and indefinite in outline. There was some cloudiness of the right apical region suggestive of tuberculosis.

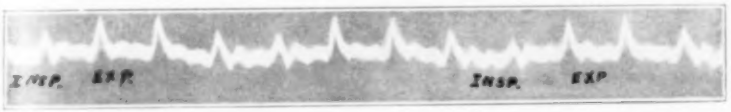

Fig. 5.—Pulsus paradoxus in a case of encapsulated paramediastinal effusion (Case 7). Pulse recorded as in Figure 1.

Course of Illness.—The diagnosis of pericardial effusion was made on the basis of the large area of cardiac dulness and the pulsus paradoxus. The rather unusual left-sided situation of the effusion was attributed to dense pleural adhesions. As the patient's cardiorespiratory symptoms were becoming more urgent, paracentesis was indicated. Accordingly, he was tapped in the left fourth intercostal space 5 cm. from the margin of the sternum, and 650 c.c. of serous exudate were removed. The paradoxical character of the pulse was markedly diminished by this procedure, and the subjective symptoms temporarily improved.

During the eight weeks that the patient was in the hospital, it was necessary to tap him every four or five days to give relief from steadily progressing symptoms of circulatory embarrassment. An average of 600 c.c. of serous fluid were withdrawn each time. Two days prior to his death, which occurred on Nov. 16, 1921, he was tapped again to relieve the urgent symptoms of cyanosis, air hunger, edema "brust beklemmung," etc., which Kussmaul [2] described as the terminal condition in his patients. The result of this procedure is given in Table 5. Figure 5 is an optical record of the pulse taken before paracentesis. Unfortunately curves were not obtained to show the pulse change afterward.

Synopsis of Postmortem Examination.—On opening the thorax, a large firmly encapsulated effusion was found in the left pleural cavity in close contact with the entire left side of the heart. The pleura was everywhere markedly thickened, especially along the mediastinum, the walls of the sac being 3 mm. in thick-

ness. The diaphragmatic pleura was completely adherent and 5 mm. thick. The right lung was completely adherent to the diaphragm and parietal pleura. Discrete tuberculosis was found at the apex of the right lung. The heart was entirely covered by the smooth, hard and greatly thickened pericardium. The pericardial sac was completely obliterated. The heart and pericardium together weighed 675 gm. The cut surface of the pericardium was composed of several layers of different character, the middle layer being yellow and structureless and the outer layers gray, fibrous and edematous. The pericardium varied from 1 cm. to 2 cm. in total thickness, being thinnest over the auricles and great vessels and thickest over the right ventricle. The myocardium was soft and brown, the wall of the left ventricle measuring 11 mm. The chambers of the heart were reduced in size. Microscopic examination confirmed the diagnosis of tuberculous pericarditis. There was found also: extensive caseous enlargement of the mediastinal lymph nodes; discrete fibrous tuberculosis of the left apex; passive congestion and edema of the lungs; chronic passive congestion of all the viscera, and nutmeg liver.

TABLE 5.—*Effect of Paracentesis of Paramediastinal Pleural Sac on Pulsus Paradoxus (Case 7); 810 C.c. Serosanguineous Fluid Withdrawn (Sp. Gr. 1.025)*

Observation	Before Paracentesis	After Paracentesis
Pulsus paradoxus	Marked*	Slightly palpable
Fluid pressure (in mm. of pleural exudate)	120-113 mm.	0-24 mm.
Pulse rate	110	120
Pulse volume	Very small	Increased
Arterial pressure	110-100 mm	110-90 mm.
Right border of cardiac dullness	2 cm. to right of sternum	At right margin of
Left border	1 cm. beyond anterior axillary line in third interspace	2 cm. within anterior axillary line sternum
Respiratory rate	32	32
Type of respiration	Mainly thoracic	Thoraco-abdominal
Vital capacity	1,500 c.c.	Not obtained
Lower margin of liver	Edge palpable at umbilicus	2 cm. higher
Neck veins	No pulsation; marked engorgement	Pulsation with less distention
General condition	Cyanosis, dyspnea, edema, very restless	Not improved

* Figure 5 shows pulse record from radial artery.

Comment.—Necropsy examination of this patient revealed a pathologic condition which was not suspected from clinical observations. What we interpreted in the physical examination as a pericardial effusion was, in reality, an encapsulated pleural effusion. From the anatomic point of view, this is an extrapericardial process, but in this case it had *by virtue of its unique relation to the heart the same physiologic effect as a pericardial effusion,* as indicated by the marked improvement in the pulse following paracentesis.

It is important, however, to consider the influence of the obliterative pericarditis which was also present in this case. Although removal of the fluid did not cause complete disappearance of the pulsus paradoxus, it had a pronounced effect in modifying the phenomenon. Consequently, we may state that of the factors concerned, the evidence strongly indicated that the primary rôle was played by the paramediastinal effusion.

GENERAL COMMENT

The foregoing cases illustrate the intimate relationship existing between pericarditis and the pulsus paradoxus. Our studies of these patients confirm the generally accepted opinion that cicatricial mediastinopericarditis is responsible for the paradoxical pulse in certain cases. An analysis of the hospital necropsy reports wherein adhesive pericarditis was present with no previous clinical evidence of a pulsus paradoxus strongly suggested to us that the absence of this physical sign in such cases was due to lack of adhesions to mobile portions of the thorax.

The observations made on paracentesis of the pericardial sac demonstrated quite conclusively that the effusion in these patients was directly responsible for the production of pulsus paradoxus. It is well known, however, that cases of pericarditis with effusion may not be associated with this pulse irregularity, and we have observed such patients. These exceptions can be accounted for by the fact that the quantity of fluid in these cases is not sufficient to raise the *pressure* within the sac to an effective level. Thus, under the conditions of a diseased and dilated sac, a surprising amount of fluid may be present without producing a pulse variation. The critical factor, we believe, is the degree of increased intrapericardial tension, which in turn is dependent on the thickness and distensibility of the parietal pericardium. The exact manner in which the pulsus paradoxus is produced under such circumstances will be analyzed more completely in the report of our animal experiments.

The striking clinical contrast which these cases afford when compared with those of Group I has been repeatedly emphasized in our case reports. In few cases of pericarditis did we find the evidence of a marked increase in pleural pressure variations such as was exhibited in the pathologic respiratory conditions. To find a person with no apparent respiratory discomfort exhibiting a definite respiratory waxing and waning of the pulse is in our experience strongly indicative of pericardial effusion.

Summary and Conclusions

1. Opportunity was afforded during the routine examination of a considerable number of patients to observe many instances of a respiratory variation in pulse amplitude. The frequency with which it was encountered in certain clinical conditions stimulated an attempt to evaluate its diagnostic importance.

2. In this report we have offered a definition of pulsus paradoxus which restricts the phenomenon to a simple respiratory waxing and waning of the pulse found under ordinary clinical circumstances. Cases

exhibiting the pulsus paradoxus are classified under two groups; the one associated with abnormal conditions of the respiratory system, and the other with pathologic affections of the pericardium.

3. The suggestion is made, chiefly on the basis of experimental work given in the following paper, however, that the pulsus paradoxus associated with abnormal conditions of the respiratory tract is primarily caused by modifications of the intrapleural pressure variation. A clinical estimate of abnormal variations in intrapleural pressure may be obtained by analysis of the mechanism of breathing.

4. Pulsus paradoxus was found in cases of mediastinopericarditis with thoracic adhesions.

5. Clinical studies proved conclusively that effusion into the pericardial sac is directly responsible for a striking manifestation of the paradoxical pulse as evidenced by the disappearance of the pulse phenomenon after tapping the sac. The essential factor required to produce this phenomenon appears to be the increase in intrapericardial tension.

6. The unusual feature of pulsus paradoxus associated with pericardial effusion is its singular occurrence in patients presenting no clinical evidence of respiratory discomfort.

7. We therefore conclude that a pulsus paradoxus unaccompanied by exaggerated respiratory efforts may be regarded as a diagnostic sign of pericardial effusion.

OBSERVATIONS ON PULSUS PARADOXUS (WITH SPECIAL REFERENCE TO PERICARDIAL EFFUSIONS)

II. EXPERIMENTAL *

L. N. KATZ, M.D., AND H. W. GAUCHAT, M.D.

CLEVELAND

In the preceding report [1] which deals with pulsus paradoxus as observed in the clinic, it was pointed out that this pulse is of some diagnostic value, provided it is properly interpreted. Pulsus paradoxus was defined as a rhythmic pulse occurring in natural breathing which shows a waxing and waning in size during respiration, evident on palpation in all the accessible arteries. A classification of pulsus paradoxus was given, and emphasis was laid on its occurrence in large pericardial effusions. In the course of the foregoing study, several questions arose which could not be satisfactorily answered by the clinical data. For instance, we were unable to determine which circulatory changes are responsible for the pulse phenomenon, and we were certain neither of the factors involved nor of how such alterations in circulation take place.

Experimental studies of pulsus paradoxus are conspicuously few. In a careful review of the literature, only three such attempts were found. In 1878, Riegel and Tuczek [2] obtained a waxing and waning of the pulse by experimentally obstructing the trachea. Rosenbach,[3] in 1886, observed a variation in pulse size when he injected large quantities of oil into the pleural sac, and also when he inflated a balloon previously inserted into the pleural cavity. Hoke,[4] in 1912, repeated the experiments of Riegel and Tuczek and obtained similar results. Moreover, he noted a decrease in the pulse when he applied traction on the pericardium and also when he compressed the superior vena cava. His deductions are open to criticism, because the evidence which he presented is incomplete.

In the present report we give the observations and conclusions obtained on reproducing this pulse phenomenon experimentally in nineteen dogs. A pulsus paradoxus was produced in various ways but always with the view of reduplicating the clinical conditions as much as practicable.

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* From the Physiological Laboratory, Western Reserve University, School of Medicine.

1. Gauchat, H. W., and Katz, L. N.: Arch. Int. Med., this issue, p. 350.
2. Riegel, F., and Tuczek, F.: Berl. klin. Wchnschr. **15**:739 and 771, 1878.
3. Rosenbach, O.: Arch. f. path. Anat. u. Physiol. **105**:215, 1886.
4. Hoke, E.: Wien. klin. Wchnschr. **25**:998, 1912.

I. EXPERIMENTAL OBSERVATIONS PERTAINING TO THE PULSUS PARADOXUS IN CHRONIC ADHESIVE MEDIASTINOPERICARDITIS

Clinicopathologic studies have shown clearly that dense adhesions extending between the heart and the thoracic parietes are frequently associated with pulsus paradoxus.[1] There has been some controversy, however, as to whether or not this pulse phenomenon occurs only when the adhesions are attached directly to the large blood vessels. In fact, it is not quite clear whether or not kinking of the various vessels is equally effective. The effect of adhesions as found in clinical cases was simulated experimentally by applying traction to the pericardium and by compressing the various vessels arising from the heart, namely, the ascending aorta, pulmonary artery, pulmonary veins and the venae cavae. The effect of these manipulations on the carotid pulse was observed, particular attention being given to the time interval elapsing before the change in the pulse was apparent.

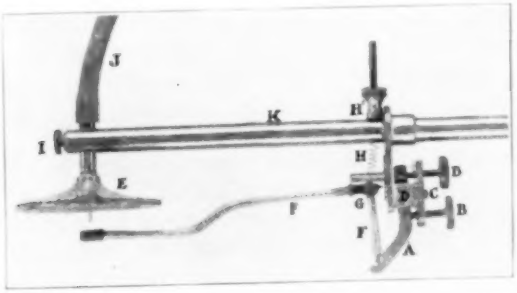

Fig. 1.—Pulse recorder (one-third of actual size). The carotid artery dissected free and in situ is placed in the groove of the lower end of the rod (*A*), which is adjustable by means of two set screws (*B*) placed in bar (*C*) on either side of fulcrum (*D*). The lateral excursion of the artery is transmitted to the cup tambour (*E*) by means of an L-shaped aluminum bar (*F*) swinging on a knife edge fulcrum (*G*). The tension of the lever is adjusted by means of screw and spring (*H*, *H'*). The cup tambour can be lowered or raised, its position being fixed by set screw (*I*) which is fastened into the supporting bar (*K*). (*J*) is the tubing which transmits the pressure changes in the tambour to an optical segment capsule.

Method.—For this purpose, the animals were anesthetized with morphin and chloretone, and artificial respiration was instituted, and the entire thoracic cage opened. The various tractions and compressions were manually performed during the apnea which followed slight overventilation of the animal.

Most of the records were obtained optically, although the earlier ones were taken on a smoked drum. The moment of manipulation was at first marked on the drum by one of us as signaled by the other. In

order to make the results more accurate, an electric signal was used later. The pulse was registered in several ways. The smoked drum tracings were recorded by connecting a Hürthle manometer with the carotid artery. The optical records were obtained with segment capsules either through the agency of a pulse recorder (Fig. 1) constructed on the same principle as the model devised by Wiggers and Baker [5] for clinical records of the radial pulse or with the aid of an arterial plethysmograph similar to the one described by Van Zwaluwenberg and Agnew.[6]

Results.—Obviously, manipulation of the aorta resulting in its partial occlusion is always followed by an immediate change in the carotid pulse. The alteration in pulse size which follows compression (or release of compression) of the pulmonary veins is not apparent at once but in the first or second beat after the manipulation. As a rule, it was found that if the manipulation occurs during systole of the ventricle or

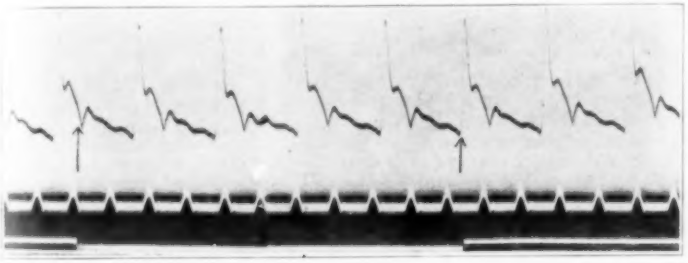

Fig. 2 (Exper. 311-16).—Record of carotid pulse showing the effect of manipulating the right pulmonary veins. Downward movement of base line in this and the following figures indicates the moment of compression, and the upward movement the moment of decompression. These points are also indicated by arrows. Pulse recorded by plethysmographic method. Time in tenths of a second.

during early diastole, the effect is apparent in the next beat, as shown in Figure 2. However, if the manipulation occurs late in diastole, the change is not noticed until the second beat, as illustrated in Figure 3. The effect of pinching the pulmonary artery is also apparent in the systemic pulse after the first or second beat. Manipulation of either of the venae cavae does not produce such an abrupt response, the pulse change not appearing until the third (as in Fig. 4) or fourth beat following the compression.

Interpretation.—The time intervals between manipulation of the various vessels and the effect on the carotid pulse are summarized diagrammatically in Figure 5. The decrease in the pulse following com-

5. Wiggers, C. J., and Baker, W. R.: Am. J. Physiol. **59**:454, 1922.
6. Van Zwaluwenberg, J. C., and Agnew, J. H.: Heart **3**:343, 1912.

pression of the pulmonary veins is obviously due to the fact that this compression immediately diminishes the supply of blood to the left side of the heart and indirectly the next ventricular discharge. This response to compression of the pulmonary veins is delayed until the second beat, when the manipulation occurs in the last part of the ventricular diastole because the ventricle at this time is already filled to

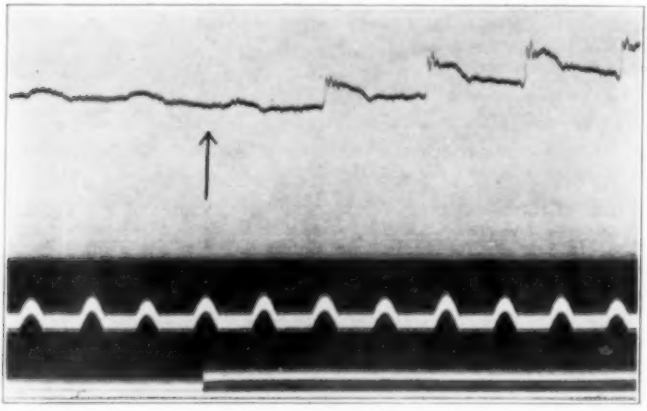

Fig. 3 (Exper. 311-9).—Record of carotid pulse showing the effect of decompression of the pulmonary veins. Pulse obtained by means of the pulse recorder shown in Figure 1.

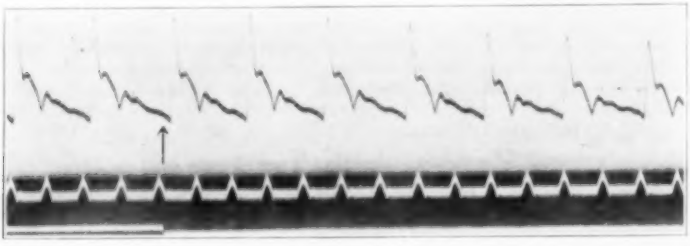

Fig. 4 (Exper. 311-15).—Record of carotid pulse, obtained as in Figure 2, showing the effect of compressing the inferior vena cava.

capacity. The longer delay which follows compression of the venae cavae is due to the added time interval required for the altered blood flow to pass through the pulmonary circuit and reach the left side of the heart.

Traction on the Pericardium.—It was found that when sufficient traction is used on the pericardium, a change in the pulse size occurs in the first or second beat after the traction is applied. The time at

which the change appears in the pulse suggests that the effect is produced by kinking either the pulmonary vessels, the aorta or both—and not by partial obstruction of the venae cavae.

It is noteworthy that this time interval is the same as that found in clinical cases of pulsus paradoxus associated with mediastinopericardial adhesions. We are therefore justified in concluding that in such patients inspiration causes a kinking in the pulmonary vessels, the aorta or both.

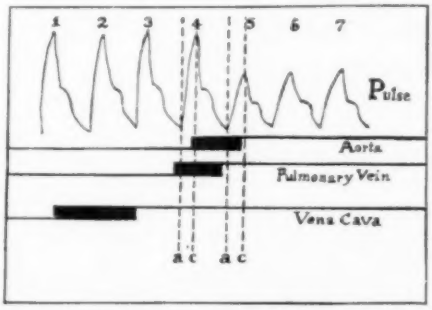

Fig. 5.—Diagram showing the time relation between compression of the various blood vessels and the appearance of the effect in the pulse: (*a*), marks the beginning of the anacrotus; (*c*), the beginning of the catacrotus. Blocks indicate time limits within which compression must occur in the respective vessels in order to produce a decrease in the size of the fifth pulse beat.

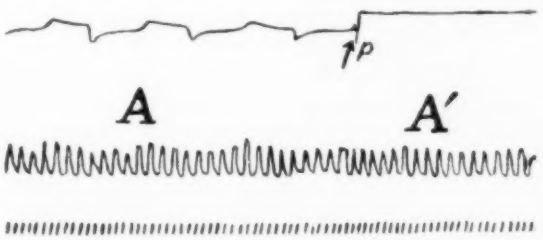

Fig. 6 (Exper. 304 0, 0′).—Tracing showing the effect of manipulating the diaphragm on the carotid pulse during apnea, when the thorax was closed (*A*) and after bilateral pleural fistulae were made (*A′*). The time at which the fistulae were made is indicated by the arrow. The upper curve indicates the intrapleural pressure; downstroke, inspiration; lower curve, carotid pulse recorded with Hürthle manometer; *p*, corresponding points. Time in tenths of a second. In *A*, intrapleural pressure varied from —40 mm. of saline to —10 mm.; in *A* the intrapleural pressure was 0 mm.

We do not infer by this that an inspiratory obstruction of the venae cavae does not occur, but that the effect of this on the pulse is probably always overshadowed by the more immediate effect of the inspiratory kinking of the other vessels. Whether the change in pulse size in some

cases is due to kinking of the aorta and in others to partial occlusion of the pulmonary vessels, or whether these two causes share equally in all cases, cannot be decided by studying the pulse. Our observations do show, however, that the adhesions need not be attached to any particular vessel but may be fastened anywhere between the cardiac structures and the thoracic parietes and still be capable of producing a pulsus paradoxus.

II. EXPERIMENTAL OBSERVATIONS PERTAINING TO THE PULSUS PARADOXUS IN EXAGGERATED BREATHING

Clinical investigation has shown conclusively that exaggeration of the depth of breathing is a common cause of pulsus paradoxus;[1] and the pulse phenomenon in this condition has been commonly attributed to an increased variation of intrapleural pressure (Baumler,[7] Reichmann,[8] Semerau,[9] Wenckebach[10]). However, a few writers have taken exception to this. Gaisböck,[11] for instance, thought it was a nervous phenomenon, and Rosenbach[2] believed that it was due to a kinking of the inferior vena cava by the inspiratory contraction of the diaphragm. In the present report, the various factors in respiration which are known to exert an influence on the circulation were therefore considered individually in order to ascertain which of them is primarily responsible for the pulsus paradoxus.

After determining what we believe to be the chief respiratory factor, the next problem was to decide the manner in which it acts on the circulation. In the past, the paradoxical pulse has been ascribed to alterations in the capacity and resistance of the intrapulmonary vessels (Hoke[4]), to modifications of the venous flow into the chest (Schreiber[12]), to changes in the capacity of the aorta and intrathoracic arteries (Reichmann[8]), and to variations in the venous return to the left side of the heart (Baumler[7]). An accurate study of the time factor, that is, the relation of pulse changes to the respiratory cycle, will eliminate most of these. In the preceding section, it was pointed out that the time interval between manipulation of the large blood vessels and the effect on the pulse is different in the various vessels concerned, but characteristic for each. The place in the circulation at which the changes primarily responsible for the paradoxical pulse occur can therefore be determined by noting with which of these time relationships the pulse phenomenon coincides.

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10. Wenckebach, K. F.: Ztschr. f. klin. Med. **71**:402, 1910.
11. Gaisböck, F.: Deutsch. Arch. f. klin. Med. **110**:506, 1913.
12. Schreiber, J.: Arch. f. exper. Path. u. Pharmacol. **12**:168, 1880.

Method.—Natural respiration and the closed chest was used in most instances. The depth of respiration was increased by asphyxiating the animal, by producing a partial pneumothorax or, in most cases, by partial tracheal obstruction. The hyperpneic stage of Cheyne-Stokes respiration, which fortunately developed spontaneously in several animals, was also available. The pulse was recorded as before. Records of respiration were obtained, except in a few cases, by means of a pleural cannula, which was connected by a T-tube both to a tambour writing on a smoked drum (or to a segment capsule in the optical tracings) and to a U-tube saline manometer. Direct readings of the latter were obtained before the tracing was inscribed, in this way giving the actual values of the intrapleural pressure. The tube leading to the manometer was closed when a record was taken in order to avoid distortion of the respiratory curve.

Relation of Changes in Size of Pulse to Depth of Respiration.—As a rule, no pulse inequality was apparent under control conditions. In some dogs, however, slight variations in pulse size occurred even with natural unexaggerated breathing, particularly in those animals which were severely traumatized or had been under deep anesthesia for some time. In all cases increasing the depth of breathing augmented these variations or induced a waxing and waning in the pulse when none had been present before (Figs. 7 *A* and *B* and 8). In general, the amount of variation in pulse size was proportional to the depth of breathing, provided other conditions remained unchanged. As a rule, the more deficient the circulation the less the extent of intrapleural pressure variation necessary to produce a pulsus paradoxus, confirming our clinical observations.[13]

The Respiratory Factor Responsible for the Changes in Pulse Amplitude.—1. Intra-Abdominal Pressure: Elimination of intra-abdominal pressure variations by opening the abdomen was not sufficient to prevent the occurrence of a pulsus paradoxus. For example, in the first half of Figure 7 *C*, the paradoxical pulse was produced by the hyperpnea resulting from partial pneumothorax. The fact that the abdomen had been previously widely opened in this animal did not prevent the appearance of the pulse phenomenon.

The unimportance of intra-abdominal pressure was further demonstrated by comparing the effect of abdominal and thoracic breathing on the pulse. Abdominal breathing was favored by restricting manually the expansion of the chest, and thoracic breathing by restricting the

13. In addition to the change in pulse amplitude, the pressure records show a fluctuation of the diastolic pressure (base line), the extent of which parallels the degree of variation in pulse size. Wiggers' tracings obtained from the pulmonary artery show somewhat similar changes (Wiggers, C. J.: Am. J. Physiol. **30**:233, 1912).

abdominal movements. In these experiments, it was found that neither type of breathing produced any changes in pulse size except when the depth of breathing was increased; and in the latter case, the pulse change occurred regardless of which type of respiration was increased.

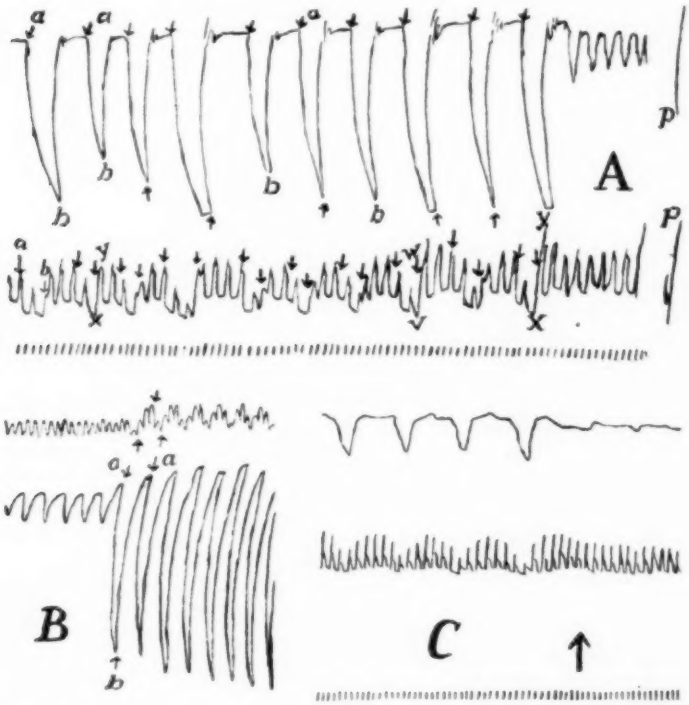

Fig. 7.—Segment A, Exper. 304 *G*: The first portion of tracing shows the effect of tracheal obstruction on the carotid pulse; the last portion is a control after release of obstruction. The upper tracing indicates intrapleural pressure; upstroke, inspiration; downstroke, expiration. The lower curve indicates the carotid pulse recorded as in Figure 6. Time in tenths of a second. P, comparable points; a, beginning of inspiration; b, beginning of expiration; other lettering explained in text.

Segment B, Exper. 302 *F* and *G*: The last portion of the tracing shows the effect of tracheal obstruction on the carotid pulse; the first portion is a control; upper curve, carotid pulse; lower curve, intrapleural pressure. Lettering as in segment A.

Segment C, Exper. 304 *P*, *P'*: The first portion of the tracing shows the effect of an induced partial pneumothorax on the carotid pulse in an animal with an open abdomen and closed thorax whose pericardium contained 90 c.c. of oil under 30 mm. of positive pressure. Intrapleural pressure varied from —80 mm. saline to —40 mm. at the time that the first portion of the curve was obtained. The second portion was taken after bilateral pleural fistulae were made; intrapleural pressure, 0 mm. The arrow indicates the point at which the holes were cut in diaphragm. Upper and lower curves as in segment A.

2. Diaphragm: Our findings in regard to the diaphragm are shown by the following typical experiments. Experiment 304 0, 0′ (Fig. 6) was performed on an animal with the thorax intact but with opened abdomen. During a period of apnea which followed slight overventilation, the central tendon of the diaphragm was grasped on its under surface and its position rhythmically changed, simulating in this way its normal respiratory excursion. A slight variation in pulse size resulted as shown by the pulse curve in tracing (*A*), but it was associated with a slight variation in intrapleural pressure (upper tracing). The excursion of the diaphragm, however, failed to produce any variation in pulse size (*A′*) after the pleural pressure variations were eliminated by bilateral pleural fistulae.

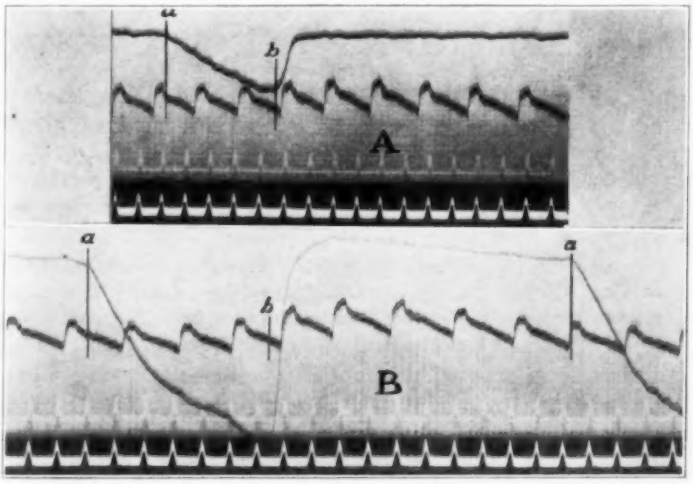

Fig. 8 (Exper. 309-4, 7).—Optical record showing the effect of partial tracheal obstruction on the carotid pulse. *A* indicates control; *B*, partial tracheal obstruction; upper curve, intrapleural pressure; downstroke, inspiration; lower curve, carotid pulse obtained with pulse recorder shown in Figure 1. Time is shown in tenths of a second. Lettering as in preceding figure. In *A*, the intrapleural pressure varied from —16 to —56 mm. of saline and in *B* from —10 to —160 mm.

Experiment 303, A, was performed on an animal in whose thorax windows 4 inches (10 cm.) in diameter were made in order to eliminate intrapleural pressure variations as well as changes in lung volume. Violent movements of the diaphragm occurred in this animal as a result of asphyxia, and yet no change in pulse amplitude appeared in the tracing.

Experiments, of which these are typical examples, indicate that, contrary to the opinion of Rosenbach,[3] the diaphragm is not the essential factor responsible for the pulsus paradoxus.

3. Lung Volume: The effects of changes in lung volume on the circulation which have been extensively studied by Cloetta leave no doubt that the resistance and capacity of the intrapulmonic vessels vary during respiration (Wigger [13]). The present investigation is concerned with the effect of these changes on the peripheral pulse.

Moderate artificial respiration was found to produce a variation in pulse amplitude in animals when the chest was closed, but none when the thorax was open. For example, in experiment 307, B and C, mild artificial respiration produced some variation in the size of the pulse when the thorax was closed. This was eliminated when the ribs were resected. In Experiment 303, B and C, the pulse was uniform in size when mild artificial respiration was instituted in the presence of open, bilateral pleural fistulae, but when the fistulae were closed a respiratory variation in pulse size appeared. Experiments such as these demonstrate that a moderate variation in lung volume per se does not affect the systemic pulse.[14]

4. Intrapleural Pressure: Thus, by a process of elimination, we are left with intrapleural pressure as the respiratory factor which produces the pulse phenomenon. A consideration of the foregoing presentation shows that elimination of the respiratory variation in intrapleural pressure was always followed by the disappearance of any previously existing variation in pulse amplitude. Another example of this is shown in Figure 7 *C*. A pulsus paradoxus was produced in a naturally breathing animal by inducing a partially closed pneumothorax (first part of Fig. 7 *C*). At the point indicated by the arrow, two large holes were made in the diaphragm. This procedure eliminated the intrapleural pressure fluctuations (upper tracing) and at the same time the inequality of the pulse (lower curve), and yet, while the record was taken, the animal breathed as before.

We therefore conclude that the respiratory factor primarily responsible for the pulsus paradoxus in exaggerated breathing is the fluctuation of intrapleural pressure.

Time Relation of the Change in Pulse Size to the Respiratory Phases.—The changes in the pulse are illustrated in Figure 7 *A*, which was obtained in a dog during marked tracheal obstruction. The results in this experiment are typical of those found throughout, although more marked than usual. This figure, as well as Figures 7 *B* and 8, shows that the changes in diastolic pressure (base line of pulse

13. Wiggers, C. J.: Physiol. Rev. **1**:239, 1921.

14. Large variations in lung volume, as is generally recognized, produce changes in the size of the pulse in open chested animals. For example, in Experiment 307, F, in which the lung volume during inflation was about twice that during deflation, a noticeable variation in pulse size was observed. Such extreme changes in lung volume probably never occur clinically or in animals with closed chests.

curve) coincide with the onset of changes in intrapleural pressure and are in the same direction and roughly proportional. This exact coincidence of the changes of diastolic pressure with the phases of respiration indicates that these changes are due to an effect on the aorta and intrathoracic arteries, in that manipulation of the ascending aorta gave a like relationship (note Fig. 5). The sudden increase in intrapleural pressure during expiration causes a rapid expulsion of blood from the chest and therefore a coincident sharp rise of diastolic pressure. When the effect of expiration is synchronous with the upstroke of the pulse, a larger pulse wave results, for example, *x*-*y* in Figure 7 *A*. This larger pulse has often been erroneously interpreted as an increased systolic discharge of the heart, the respiratory factor being overlooked. A similar effect on the pulse can be readily produced by coughing, and such records were obtained by us on several occasions.

With regard to pulse size with which we are primarily concerned, the change does not coincide with the beginning of the phase of respiration but occurs either in the first or second beat after its onset. Thus, when the beginning of expiration comes early in diastole, as in Figure 8, and in the third, fifth, sixth and seventh expiration in Figure 7 *A*, the next beat is larger. When the onset of expiration comes late in the diastole or at the onset of the systole, as in the first, fourth and ninth expirations in Figure 7 *A*, the increase in pulse beat is not apparent until the second beat. Finally, when expiration begins with ventricular ejection, the resulting beat is larger, owing to a summation of ventricular ejection and the effect of the sudden expiration on the aortic capacity, as pointed out above. Analysis of the curves presented will show a like time relationship at the beginning of inspiration. Expiration was selected in the foregoing discussion only because it brings out the changes in a striking manner.

The Significance of the Temporal Relationship.—The time relation found in exaggerated breathing coincides with that found on manipulating the pulmonary veins (as will be seen on comparing the observations outlined above with the diagram, Fig. 5), indicating that the variation in pulse amplitude in this condition is due directly to a modification of the venous return to the left ventricle.

Further confirmation of this interpretation is given by the fact that a similar relationship between pulse and respiration was found in this series, regardless of the number of beats per respiratory cycle. In fact, a similar relationship was found in our clinical cases, in which an even wider range of respiratory and pulse rates was obtained. Furthermore, in clinical cases (and animal experiments) in which Cheyne-Stokes respiration appeared, the first inspiration coming after an apneic period was associated with a decrease in pulse size, which began in the beat following the inspiration.

The last observation excludes the possibility of the pulsus paradoxus being due to a delayed effect of alterations in venous flow to the thorax, as has been argued by some, because such a hypothesis would not explain the immediate decrease in the pulse following inspiration after a long period of apnea.[15] The fact that the changes in pulse size do not coincide with the variations in diastolic pressure suggests that the changes in the pulse amplitude are not due to variations in the capacity of the aorta.

The changes in venous flow to the left ventricle can best be attributed, we believe, to an alteration in the capacity of the pulmonary veins. A change in the pressure around a tube which is open at both ends causes not only a like change in the pressure within, but also an opposite change in the caliber of the vessel. These changes are not proportional, however, but their extent depends on the character of the vessel wall. During respiration one would therefore expect a variation in the size of the pulmonary vessels, particularly the veins. This was found to be true by de Jager,[16] who demonstrated a decrease in the capacity of the pulmonary vessels during expiration and an increase during inspiration, the changes being much greater in the pulmonary veins than in the pulmonary arteries. As the pulmonary veins increase in size during inspiration, part of the blood passing through them is retained to fill the widened channels, and less reaches the left side of the heart. During expiration the pulmonary veins decrease in size and the blood that had been, so to speak, stored in them during inspiration now augments the venous flow to the heart. Respiration always has this effect, but it is only when it is greatly accentuated that enough alteration in the ventricular filling and discharge is obtained to cause a pulsus paradoxus.

According to this conception, the amount of change in intrapleural pressure is important, but much more important is the velocity with which the pressure varies. It is apparent that the amount of blood delivered to the left side of the heart during apnea is equal to the amount entering the pulmonary veins from the pulmonary capillaries. A discrepancy occurs only when the vessels are changing in caliber, and the degree of discrepancy will obviously depend on the rapidity of the alteration in the size of the vessels or, in other words, on the velocity with which the intrapleural pressure is modified. This dependence of the changes in pulse size on the velocity of respiration has actually been found in our clinical cases, and an analysis of the animal experi-

15. The relationship found in Cheyne-Stokes breathing can be demonstrated readily by having a person hold his breath with the chest in midposition as long as possible and noting the pulse when he first inspires. It will be found that the pulse decreases in the beat that follows the beginning of inspiration.

16. De Jager, S.: Arch. f. d. ges. Physiol. **20**:426, 1879.

ments showed it to be true here also—as will be seen when one compares the effect of inspiration and expiration in Figure 7 *A* and 8 from this point of view.

The explanation suggested above seems to us to be the most logical account for the facts observed. None of the others which we have considered in the course of this study fit the facts so well.

III. EXPERIMENTAL OBSERVATIONS PERTAINING TO THE PULSUS PARADOXUS IN PERICARDIAL EFFUSIONS

The pulsus paradoxus as observed in clinical cases with pericardial effusions was discussed in the preceding paper.[1] A feature of the paradoxical pulse under these circumstances was the fact that it was not accompanied by any extraordinary efforts of breathing. It seemed rather remarkable that patients with ordinary tranquil respiration should show such a respiratory variation in the size of the pulse. Consequently, it was apparent that some factor other than an increased intrapleural pressure variation was the cause of the pulse phenomenon. Pericardial effusions were accordingly reproduced in animals in order to determine the nature of this factor.

Pericardial effusions have been used to study the circulation in a variety of ways by a number of observers. Cannon and Cattell,[17] for instance, used it in their researches on shock. Hoke [4] observed a variation in the size of the pulse when fluid was injected into the pericardium of a rabbit. Starling,[18] on injecting oil into the pericardium, found among other things that the arterial pressure fell and the venous pressure rose. Lewis,[19] using small cats, noted that a slight rise in pericardial pressure caused a disproportionate fall in arterial pressure. Although the methods used by these investigators were satisfactory for their purposes, they did not faithfully reproduce all the conditions found in clinical cases of pericardial effusion.

Method.—A technic was developed by which an infusion could be produced in a naturally breathing animal with closed chest. Dogs were anesthetized as before; a pleural cannula was inserted into the pleural sac, and the inspiratory and expiratory pressures were noted in the manner already indicated. Tracheotomy was then performed and artificial respiration instituted. A 4-inch (10 cm.) vertical incision was made over the lower part of the left side of the chest in the parasternal line and the ribs exposed. Two or three ribs were then resected for a distance of 3 inches (7.5 cm.) and the parietal pleura incised. A window was thus made into the pleural cavity. The parietal pericardium near the cardiac

17. Cannon, W. B., and Cattell, McK.: Experimental Traumatic Shock; Critical Level in a Falling Blood Pressure, Arch. Surg. **4**:300 (March) 1922.
18. Starling, E. H.: Lancet **1**:652, 1897.
19. Lewis, T.: J. Physiol. **37**:233, 1908.

apex which appeared medial to the opening was next grasped with several hemostats and brought out through the window. A half inch (1.25 cm.) incision was now made in the pericardium and a loose silk purse-string suture run around the opening. Into this the flanged end of a specially constructed brass cannula was inserted; the purse-string suture was tightened and tied and the collar screwed down. A non-leakable connection was made in this way, which was confirmed by a postmortem examination on every preparation.

The cannula was connected to a manometer by means of rubber tubing. After the pericardium was replaced, this tubing was brought out through the hole in the chest. Enough tubing was left in the chest to permit unhampered movement of the heart. The window in the chest was closed by stitching the ribs, muscle flaps and skin in place. Several pieces of petrolatum soaked gauze were inserted between the various layers in order to make the closure air tight.

The lungs were markedly inflated so as to obliterate the pleural space and expel the air in it through the pleural cannula which was then connected to a tambour (or segment capsule) and manometer as described before. The intrapleural pressure was again read after the artificial respiration was stopped and natural breathing resumed. It was our experience that when the wound closure was air-tight the intrapleural pressure readings were approximately the same as before the operation.

In the early experiments oil (bland paraffin) was injected into the pericardium by means of a T-tube inserted into the tube connecting the pericardium to the manometer. In the later experiments, physiologic sodium chlorid solution was used. The pericardial pressure was read in millimeters of oil or saline solution depending on which was utilized. The difference in specific gravity between the two was not great enough to require correction, at least for our purposes; the lower viscosity of the saline solution permitted more accurate readings of the variations in pressure, however. In some of the experiments the pericardial pressure was optically recorded with a fair degree of accuracy by connecting the top of the pericardial manometer to a segment capsule.

The pulse and respirations were recorded as before. Venous pressures were read directly by means of saline manometers, which were connected to sounds inserted into the external jugular veins. On the right side, the sound was inserted so that the opening in it was within the pericardium, that is, in the right auricle. The sound in the left innominate vein was placed just within the thorax, so that its open end was without the pericardium. The position of the sounds was of course confirmed at necropsy, and corrections were made for the zero level. As will be pointed out later, we were interested in simultaneous readings of the two pressures, so a device was constructed to permit this.

A stop cock was inserted in each circuit and so arranged as to be operated by a single lever. Thus, when a reading was desired at the end of inspiration (or expiration) it was obtained by turning the lever at the proper moment, thereby interrupting both circuits at the same time.

Effect of Experimental Pericardial Infusion on the Pulse.—The first effect noted on injecting fluid into the pericardium was a decrease in the size of the pulse and a fall in the blood pressure—mean, systolic and diastolic (Fig. 9); but the most striking change was the appearance of a pulsus paradoxus. The injection of fluid caused a waxing and waning in the pulse or markedly accentuated one already present (Figs. 9 and 10). The degree of these changes was found to be proportional to the pressure developed in the pericardial sac. Sometimes the paradoxical pulse appeared as soon as fluid was injected; at other times, only after a moderate degree of pressure was developed. Furthermore, the degree of the pulse variation increased as the sac was

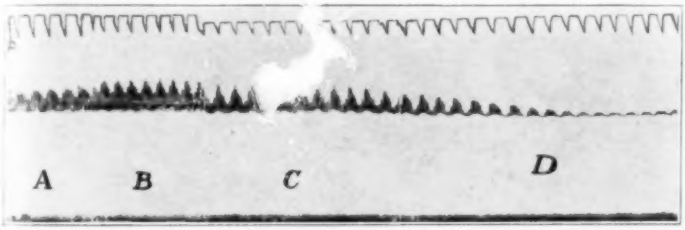

Fig. 9 (Exper. 306 *C, C'''*).—Slow smoked drum tracing showing the effect of pericardial infusion on the carotid pulse and intrapleural pressure. Segment A, control; Segments B, C and D, various stages during infusion of oil. Records obtained as in Figure 7 *A*.

			Intrapleural Pressure (in Mm. of Saline)			Bean Pericardial Pressure (in Mm. of Oil)
		C.c. of Oil in Pericardium	Inspiration, Mm.	Expiration, Mm.	Variation, Mm.	
	A.....	0	—120	—70	50	0
End of	B.....	150	—110	—80	30	+100
End of	C.....	180	—110	—70	40	+160
Middle of	D.....	195	— 90	—60	30	+300

distended with fluid until the pulse became very small, when it became less conspicuous (Fig. 9).[20]

Time Relation of the Changes in Pulse Size to the Phases of Respiration.—A careful analysis of our records, typical examples of which are shown in Figures 10 and 11 *A* and *B*, reveals a time relationship similar to that found in exaggerated breathing. The change in

20. In addition, there was less fluctuation in diastolic pressure as compared with the pulse in exaggerated breath (compare Figs. 10 and 7 *A*).

pulse size always occurred in the first or second beat after the onset of the respiratory phase, regardless of the fact that this series had a wide range of respiratory and heart rates. This time relationship indicates that the pulsus paradoxus in pericardial effusions is due directly to alterations in the venous return to the left heart in that it follows in the same period as the response to manipulation of the pulmonary vessels (note Fig. 5).

Nature of the Mechanism by Which the Venous Flow to the Left Side of the Heart Is Altered.—The mechanism producing the pulsus paradoxus in pericardial effusion resembles that in exaggerated breathing in that the pulse in this condition is also primarily due to the effect of intrapleural pressure variations, since it does not persist when the pleural pressure variations are eliminated. The mechanisms differ, however, in that a pulsus paradoxus occurs in pericardial effusions even

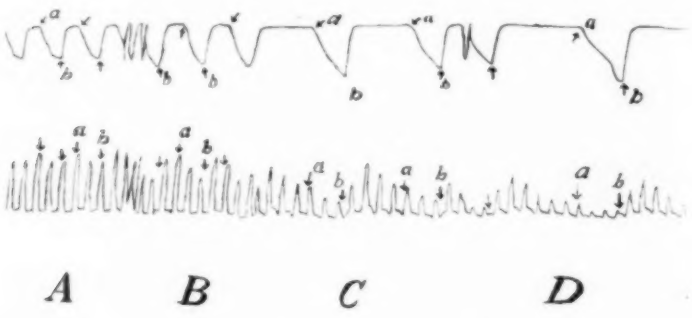

Fig. 10 (Exper. *302 H, J, L and M*). Smoked drum record showing the effect of pericardial infusion on the carotid pulse and intrapleural pressure. Curves recorded as in preceding figure; *a*, beginning of inspiration; *b*, beginning of expiration. Segment A, control, segments B to D, various stages during infusion of oil.

	Amount of Oil in Pericardium, Cc.	Mean Pressure in Pericardium, Mm. of Oil
A	0	0
B	40	+ 90
C	80	+200
D	100	+250

when the depth of breathing is not exaggerated. Reference to Figures 9 and 10 will show this to be the case, as will the data presented on this point in Tables 1 and 3. It was our experience that ordinarily the depth of breathing (as indicated by the amount of variation in the intrapleural pressure) was not increased by injection of fluid in the pericardium except when the circulation was so interfered with as to cause partial asphyxia. An example of this is shown in the upper tracing in

TABLE 1.—*Effect of Pericardial Effusion on Pressure in the Pleural and Pericardial Cavities*

1	2	3	4	5	6	7	8
		Intrapleural Pressure			Intrapericardial Pressure		
Experiment	Amount of Fluid in Pericardium	Inspiration	Expiration	Variation	Inspiration	Expiration	Variation
317-1	0*	−50 †	−28 †	22 †	−25 †	−10 †	15 †
317-5	0	−34	−16	18	−30	−12	18
317-8	0	−36	−18	18	−30	−14	16
317-2	25	−50	−20	30	+ 5	+24	19
317-3	75	−40	−20	20	+54	+60	6
317-6	75	−36	−16	20	+62	+71	9
317-7	100	−36	−12	24	+150	+160	10
317-4	105	−40	−20	20	+160	+165	5

* Cubic centimeters of saline solution injected.
† Millimeters of saline solution.

TABLE 2.—*Effect of Varying the Pressure About the Excised Pericardium on the Pressure Within It*

	Pressure Around Pericardium, Mm.†	Pressure Within Pericardium			
		When Containing No Fluid	When Distended with Fluid to Varying Degrees		
		Mm.†	Mm.†	Mm.†	Mm.†
A, before partial vacuum produced.	0	0	+220	+475	+775	+960
A′, after vacuum released.....	0	0	+190	+435	+745	+970
B, on producing partial vacuum....	−200	−195	+ 90	+365	+705	+950
C, average difference of pressure*...	200	195	120	90	55	30

* Of saline solution.

* Obtained by formula $C = \frac{(A + A')}{2} - B$.

TABLE 3.—*Effect of Pericardial Effusion on the Venous Pressure*

1	2	3	4	5	6	7	8	9	10	11	12	13	14
		Pressure in Pleural Cavity, Mm. of Saline Solution			Pressure in Pericardium, Mm. of Saline Solution			Intravenous Pressure in Innominate Vein, Mm. of Saline Solution			Right Intra-auricular Pressure, Mm. of Saline Solution		
Experiment	Amount of Saline Solution in Pericardium, C.c.	Inspiration	Expiration	Variation	Inspiration	Expiration	Variation	Inspiration	Expiration	Variation	Inspiration	Expiration	Variation
319-1	10	−70	−40	30	− 50	− 25	25	− 1	− 5	6	− 15	− 12	6
319-2	0	−70	−40	30	− 50	− 20	30	− 5	− 2	7	− 20	− 15	5
319-3	0	−76	−40	36	− 45	− 20	25	− 5	− 2	7	− 20	− 15	5
319-4	60	−72	−40	32	− 5	+ 12	17	+14	+18	4	+ 1	+ 5	4
319-5	120	−70	−40	30	+ 50	+ 60	10	+60	+64	4	+ 63	+ 65	2
319-6	120	−70	−40	30	+ 50	+ 60	10	+59	+64	5	+ 63	+ 65	2
319-8*	0	−82	−44	38	− 50	− 30	20	....	....	..	− 10	− 10	20
319-9	115	−80	−40	40	+100	+110	10	....	....	..	+112	+120	8
319-10	115	−72	−40	32	+104	+112	8	....	....	..	+115	+122	7
319-11	115	−70	−40	30	+ 99	+105	6	....	....	..	+115	+120	5

* Saline injected intravenously in interim.

Figure 9, where it will be noted that the breathing is only increased in the last part of the tracing. We can only conclude from these observations that the presence of fluid in the pericardium introduces a factor which in some way amplifies the effects of intrapleural pressure. This factor we found to be intimately associated with the intrapericardial pressure.

The Pressure in the Pericardial Sac.—We found that the elevation of intrapericardial pressure was not proportional to the amount of fluid injected. If the amount of fluid in the pericardium was increased in an arithmetic progression, the pressure was found to increase more or less in a geometric progression (note data given in Table 1 and legend beneath Figure 9). Although the pressure level in the pericardium increases as fluid is injected, that in the pleural sac remains practically unaltered because of the interposition of the parietal pericardium between these two spaces. For example, in a marked case the pressure in the pericardium rose 300 mm., whereas that in the pleural cavity increased but 20 mm. (note legend beneath Figure 9).

In addition, a striking change was noted in the respiratory pressure variations in the pericardial sac. Normally the intrapleural pressure variations are transmitted into the pericardium. However, when fluid is injected the influence of the pleural pressure variation on the pericardial pressure is diminished. These facts are apparent on analyzing the data in Tables 1 (Columns 5 and 8) and 3 (Columns 8 and 14). A marked case may be cited. The injection of oil into the pericardium of an animal caused in this instance an elevation of 100 mm. in pericardial pressure and the appearance of a pulsus paradoxus. It was found that while the intrapleural pressure showed a fluctuation of 130 mm., the pericardial pressure showed only a respiratory variation of 10 mm.[21]

The findings in this connection were somewhat unexpected, and therefore an attempt was made to verify them in other ways. Records of the pericardial pressure were obtained optically, simultaneously with the intrapleural pressure. Although the records are slightly distorted, they are accurate enough to show definitely the decrease in the amount of pressure variation. Thus, in Figure 12, which is an example of such a record, segment *A* is the control and *B* the curve when the sac was distended with saline solution. The excursion of the pericardial pressure (upper curve) is greater than the excursion of the intrapleural pressure (lower curve) in segment *A* due to the more sensitive membrane used to record pericardial pressure. It will be seen that the pericardial curve is much smaller in *B* than in *A*, although the intrapleural curve is as large as before.

21. Although part of this difference might be attributed to the viscosity of the oil, this played but a minor rôle as like differences were obtained when saline solution was used.

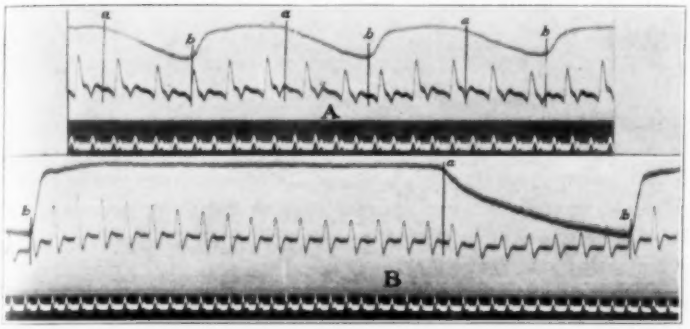

Fig. 11.—Optical records obtained while pericardial sac was distended with saline solution, showing the time relation of the pulse changes as described in text. The lower curve indicates the carotid pulse obtained with the plethysmograph; upper curve, intrapleural pressure.

Segment A, Exper. 315-4: Vagi intact; 90 c.c. of oil in pericardium; pressure in pericardium varied 9 mm. (from + 134 to + 125 mm. of saline); intrapleural pressure varied 20 mm. (from —20 mm. to —40 mm. of saline).

Segment B, Exper. 316-1: Both vagi sectioned; 100 c.c. of saline in pericardium; pericardial pressure not obtained; intrapleural pressure varied 50 mm. (from 0 to —50 mm. of saline).

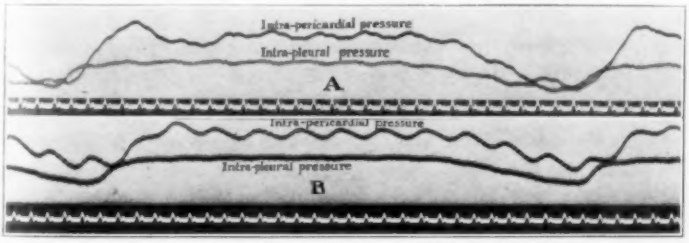

Fig. 12 (Exper. 315-10, 15).—Simultaneous optical records of intrapleural and pericardial pressures. *A*, control, no saline in pericardium; *B*, 70 c.c. of saline in pericardium. Time in tenths of a second.

	Intrapleural Pressure (in Mm. of Saline)			Intrapericardial Pressure (in Mm. of Saline)		
	Inspiration, Mm.	Expiration, Mm.	Variation, Mm.	Inspiration, Mm.	Expiration, Mm.	Variation, Mm.
A	—60	—24	36	—60	—25	35
B	—56	—16	40	+36	+56	20

As a further check, observations were also made on the excised pericardial sac where conditions could be more readily controlled. The pericardium was dissected out with the pericardial cannula in place. The various vessels were tied as they emerged from the pericardium, except the inferior vena cava and one of the pulmonary veins. The heart was distended by injecting saline solution through the latter vessels, after which they were tied. The preparation was then placed in a glass jar which could be sealed air tight. The cover of this jar had two holes, through one of which the tubing from the pericardial fistula was brought out and connected as in the living animal experiments. The other hole which communicated with the inside of the jar was connected to a manometer. A side tube was inserted in this connection, and through it the pressure in the jar was altered. The effect of changing the pressure in the jar on the pressure within the pericardial sac was observed both when the sac was undistended and also when it was distended with fluid.

The results, illustrated by a single experiment analyzed in Table 2, show that under normal conditions the changing pressures around the pericardial sac are transmitted without loss to the interior. However, when the sac is distended with fluid, the intrapericardial pressure changes are only from one-fourth to one-half as great as those on the outside. This is undoubtedly due to the relative inelasticity of the pericardium (Barnard [22]) and the fact that it rapidly reaches the limit of its elasticity as more and more fluid is forced into it. Under such conditions, comparatively slight pressure variations—either such as occur during inspiration and expiration within the chest, or even such as were mechanically produced in our "jar preparation"—are unable to stretch or compress the rigid pericardium further. Physiologically, the pericardial contents become virtually extrathoracic.

Interpretation of the Pulsus Paradoxus in Pericardial Effusion.—With these facts established, it is possible for the first time to formulate a hypothesis which logically explains the paradoxical pulse in pericardial effusion. Normally, the variations of intrapleural pressure during expiration and inspiration are transmitted without loss through the pericardium to the chambers of the heart. Consequently, the fall of intrathoracic pressure produced during inspiration affects the pressures within the auricles and ventricles about as much as the pressure in the entering extrapericardial veins. It follows that the effective difference in pressure between the veins and the heart is at least not greatly altered by the act of inspiration, and the systolic discharge is practically unaffected by this factor.

22. Barnard, H. L.: Lancet **1**:1080, 1899.

When, on the other hand, the limit of distensibility is more nearly approached by the pressure of fluid within the sac, the respiratory variations of intrathoracic pressure cannot affect intracardiac pressures as much as those in the entering veins. For example, inspiration will cause a smaller pressure fall within the auricle than within the entering veins, making the pressure gradient between these two points less in inspiration than during expiration. This must necessarily result in a reduced filling of the heart and a reduced discharge of those beats which come during inspiration, thus explaining the production of a paradoxical pulse even though a normal depth of breathing is maintained. In Figure 13, an attempt is made to express this conception graphically. Of course, only the trend of the pressure changes can be shown. If the shaded area represents the gradient of pressure between

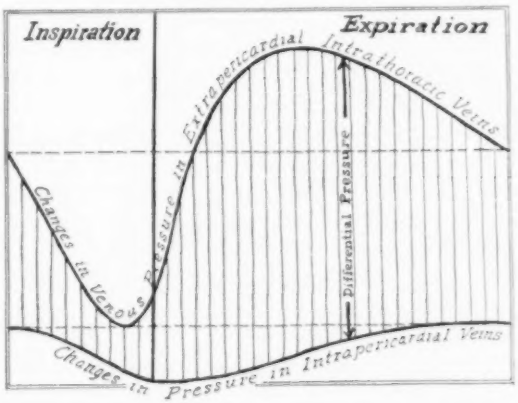

Fig. 13.—Diagram showing variations of venous pressure gradient (differential pressure) during respiration when pericardial sac is distended with fluid.

veins and auricle at different moments of the respiratory cycle, and it is recalled that the pressure difference determines ventricular filling and discharge as well as pulse amplitude, it should be clear how the waxing and waning of the pulse can be produced by pericardial effusion.

Experimental Proof of the Validity of This Hypothesis.—While this hypothesis adequately explains the production of the paradoxical pulse in accord with experimental facts, it would go far toward greater surety if it could be shown that such pressure differences as are postulated by this conception actually obtained in the pulmonary veins and left side of the heart. Experimentally, this is far more difficult and probably no more decisive than similar observations on pressures in the right side of the heart and its entering veins. A study of the pressures in the superior vena cava and auricle was therefore made in naturally

breathing animals. Two sounds were inserted into the jugular veins so that their ends rested in the right auricle and entering veins as confirmed by postmortem examination. These were connected to U-shaped saline manometers on which accurate readings could be made. Provision was also made for flooding the cannulae periodically and so keeping them free from clots.

Two successful experiments were carried out. The results of one of these are tabulated in Table 3. The data show: (1) that the introduction of fluid into the pericardial sac elevates the average pressures both in the right auricle and entering veins, and (2) that the respiratory variations of intra-auricular pressure decrease while the pressure variations in the entering veins remain unaltered. In other words, the pressure difference between the auricle and the entering veins becomes less during inspiration than during expiration.

For example, normally the venous pressure decreased from 6 to 7 mm. during inspiration, while intra-auricular pressure decreased from 5 to 6 mm. After injecting 60 c c. of saline solution into the pericardial sac, the pressure variations in both vein and auricle were 4 mm. After introducing 120 c.c. of saline solution, the venous pressure decreased from 4 to 5 mm. during inspiration, while intra-auricular pressure fell only 2 mm. At this time a distinct paradoxical pulse could be palpated and recorded.

SUMMARY

The results of animal experiments carried out in order to elucidate the causes of pulsus paradoxus as found in clinical cases may be summarized as follows:

1. Mechanical compression of the aorta produces an immediate effect on the pulse amplitude; compression of the pulmonary veins causes a decrease within one or two beats; compression of the venae cavae, however, causes no effect on pulse amplitude for three or four beats. These time relations are of paramount importance in locating the influence that is responsible for a similar reduction in pulse amplitude during inspiration.

2. Traction exerted anywhere on the pericardial structures may produce a pulsus paradoxus, the presence and degree of which depend on the tension exerted rather than on the location of the "adhesions." Time relations show that such a pulsus paradoxus is always the direct or indirect result of partial occlusion of the pulmonary vessels, the aorta, or both, and never due to compression of the venae cavae.

3. Augmented breathing experimentally produced in a variety of ways causes a waxing and waning of the pulse during expiration and inspiration. Details of experiments are given showing that this is due to increased variations in intrapleural pressure and not to traction effects. The greater the depth and velocity of these pressure changes,

the greater the effect on the pulse. Time relations show that the effect is exerted on the volume flow into the left side of the heart, and this we interpret as being due to the changing capacity of the pulmonary veins.

4. In artificial pericardial effusions experimentally produced, a pulsus paradoxus appears without change in the depth of breathing, thus simulating the clinical condition. Experiments are detailed showing that the pulse amplitude is decreased in the first or second beat after the onset of inspiration. This eliminates the possibilities that the pulsus paradoxus is directly due to an effect of inspiration on the volume of either the aorta or venae cavae, and shows that it is occasioned by the effect of variations in intrapleural pressure on the volume flow to the left side of the heart.

5. The facts established by experiments, notably (*a*) that intrapericardial pressure varies less during respiration when the sac is distended with fluid than it does normally, and (*b*) that with a distended sac intra-auricular pressure changes less during each respiratory cycle than the pressure in the entering veins, favor the following explanation of the paradoxical pulse during pericardial effusion:

With the pericardium distended with fluid, not only is the flow of blood into the heart impeded, but the inflow also varies during inspiration and expiration, owing to the fact that the respiratory variations of intrathoracic pressure do not affect the intrapericardial and intracardiac pressures as much as those in the entering veins. This causes a smaller difference of pressure between the veins and heart during inspiration and allows less filling of each ventricle. Consequently, a paradoxical pulse probably appears in both the pulmonary and systemic circuits, but obviously the arterial pulsus paradoxus is due to the impaired inflow into the left ventricle.

THE ORIGIN OF URINARY AMMONIA*

SECOND PAPER

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MONTREAL

Of the enormous amount of work done concerning the concentration of ionized hydrogen in the body fluids, much is of more than abstract interest from the clinical point of view. The recognized fact that even in disease the true reaction of the blood varies within narrow limits has led to much study of the possible factors controlling this phenomenon. It is from work on this phase of the subject that observations primarily of interest to the physical chemist only have now become of interest and importance to the clinician.

In this communication, we are concerned only with the part that the kidneys play in the regulation of the body neutrality. The literature is enormous, and recently [1] excellent reviews have appeared on the subject. Experimentally, an acidosis may be produced in man by proper changes in diet, such as restriction of carbohydrates or salts. Even under normal conditions of diet there is always a tendency toward the production of an acidosis. Thus, in the normal food of man, the acid radicals present are in excess of the basic ones. Acid formation is therefore in excess of base formation. This excess of acid radicals is eliminated by the lungs and the kidneys. The value of the study of the urinary acidity and the factors which modify it are thus apparent. The reaction of the blood varies within narrow limits, even in disease, and is nearly always alkaline (p_H 7.4). The reaction of the urine has a wider limit of variation and is nearly always acid. In normal persons [2] the urine may be as much as 400 or more times as acid (p_H 4.82) as the blood (p_H 7.45) or may be just slightly more alkaline (p_H 7.46). Though this wide variation may be noted in individual studies, in a statistical sense, under general conditions of diet and activity, the average acidity is fairly constant, p_H 6.03, or about 13 times more acid than blood. In a thorough study of the factors which account for the wide fluctuations in the acidity of normal and pathologic urines, Henderson and Palmer [2] have shown that such fluctuations are charac-

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1. Van Slyke, D. D.: The Carbon Dioxide Carriers of the Blood, Physiol. Rev. **1**:141 (Jan.) 1921. Wilson, D. W.: Neutrality Regulation in the Body, Physiol. Rev. **3**:295 (July) 1923.

2. Henderson, L. J., and Palmer, W. W.: On the Intensity of Urinary Acidity in Normal and Pathological Conditions, J. Biol. Chem. **13**:393, 1912-1913. On the Several Factors of Acid Excretion, Ibid. **17**:305, 1914. On the Several Factors of Acid Excretion in Nephritis, Ibid. **21**:37, 1915.

teristic of a phosphate mixture containing phosphoric acid and base. The base varies from the amount necessary to form monobasic to that necessary to form dibasic phosphate. A further study of the acidity and excretion of titratable acid and ammonia was made by the same authors in urines of normal and nephritic persons. They observed an increase in the intensity of the acidity of the urine in nephritis accompanied by a diminished elimination of total acid (titratable acid plus ammonia). In cardiorenal disease the average acidity (p_H 5.33) was over 100 times greater than that of the blood. For the first time they recorded a condition of acidosis accompanied by a diminished excretion of ammonia. Judging from the scanty literature on the subject, the practical clinical significance of these important observations appears to have been overlooked.

In 1921, Nash and Benedict [3] reviewed the literature and made a fundamental observation concerning the origin of urinary ammonia. The findings of these authors renew interest in the study of the excretion of the titratable acid and ammonia in the urine. Not only has the clinical value of this test become enhanced, but an additional interpretation is attached to the results. Briefly, because of the low values accepted for the concentration of ammonia in the blood, it appeared difficult to explain the amounts of ammonia at times found in urine. By calculating the amount of ammonia which could pass through the kidneys each day, it is found that a sufficient amount could not pass through to account for the amount found in the urine. As a result of animal experimentation, these authors concluded that the urinary ammonia must be formed within the kidneys. Further animal experiments by the same authors [4] seemed to substantiate this view. Studies made by Russel [5] on advanced renal disease show low values for blood ammonia and lend support to the Nash and Benedict hypothesis. The part that ammonia may play in the regulation of the reaction of body fluids is readily appreciated from certain observations on the alkali binding capacity of phosphoric acid.[1] At p_H 4.8, a urine reaction, one molecule of phosphoric acid is combined with less than one molecule of base as acid sodium phosphate. At a p_H 7.45, the reaction of the blood, one molecule of phosphoric acid is combined with about 1.8 molecules of base. Thus in the excretion of one molecule of phosphoric acid, nearly one molecule of base may be retained within the body. Another observation is that one molecule of ammonia represents the saving

3. Nash, R. P., Jr., and Benedict, S. R.: The Ammonia Content of the Blood and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, J. Biol. Chem. **48**:463, 1921.

4. Nash, T. P., Jr., and Benedict, S. R.: Note on the Ammonia Content of the Blood, J. Biol. Chem. **51**:183, 1922.

5. Russel, D. S.: The Ammonia Content of the Blood in Nephritis, Biochem. **17**:72, 1923.

of one molecule of base. The importance of the observation that the kidneys are the site of ammonia thus becomes apparent. In the presence of a kidney lesion associated with a defective mechanism for the production of ammonia, the acids formed either in health or in disease in the absence of sufficient ammonia must call on the reserve bases of the body. If the kidneys are the site of ammonia formation, the part played by them in the regulation of the reaction of the body fluids, as pointed out by Nash and Benedict, becomes clear. An acidosis may be produced either when the rate of acid production is greater than the rate of ammonia formation, as may occur in diabetes, or even under conditions of a normal amount of acid production, if the kidneys have lost the function of ammonia formation, as in nephritis.

Since the publication of the experimental work of Nash and Benedict, observations on the blood and urinary ammonia in diabetic and nephritic patients have been made in this hospital, and the estimation of the titratable acid and ammonia in the urine of diabetic patients has been practically a daily routine in all cases. The published data [6] in which the blood and urine ammonia values are correlated give clinical confirmation to the experimental work.

A study of the data obtained on the titratable acid and ammonia, which is recorded here, emphasizes the clinical importance of such determinations when considered from the point of view that the kidneys are the site of ammonia formation. Observations were made in 1,422 instances, including 112 cases of diabetes. The data are recorded below. The diabetic cases are divided into four groups, as follows:

Group 1: Cases with no nephritis (no albumin, no casts) and no ketosis

Group 2: Cases with no nephritis but with ketosis

Group 3: Cases with nephritis but no ketosis

Group 4: Cases with nephritis with ketosis

The other routine data concerning blood and urine sugar, etc., are omitted as they have no direct bearing on the present discussion. The work done in which the clinical picture and the results of the various renal function tests are correlated with the amount of ammonia excreted form part of a separate communication. The object in this article is only to show, in a statistical sense, the effect of nephritis on the excretion of ammonia and also an observation which does not appear to have been hitherto recorded in diabetes—the quantitative relation between acid and ammonia production.

It need hardly be stated that all values were obtained from complete twenty-four hour specimens of urine, collected and preserved

6. Rabinowitch, I. M.: The Origin of Urinary Ammonia, Canad. M. A. J., October 1923.

(ice and toluene) under standard conditions for metabolism work. The acid was titrated to p_H 8.5, using phenolphthalein as the indicator. The data are recorded in the tables. It will be noted that the same hospital number in some instances appears in two tables. This was done with the object of separating the urinary ammonia values in the four groups mentioned above, thus showing the effect of acid production on ammonia formation. It is generally recognized that a glance at any table in which are recorded the values of the daily excretion of total acid (titratable acid plus ammonia) shows the difficulty under which one must observe the relation, if there be any, between the production of acids and the formation of ammonia. It appears that since the reaction of the blood is fairly constant, the factors controlling the reaction must

TABLE 1.—*Urinary Ammonia in Normal Persons and in Persons with Nephritis*

Normal			Nephritic					
Case No.	No. of Determinations	Ammonia, Grams per Liter Acid	Case No.	No. of Determinations	Ammonia, Grams per Liter Acid	Case No.	No. of Determinations	Ammonia, Grams per Liter Acid
1	12	0.94	1	4	0.33	23	3	0.80
2	7	0.85	2	5	0.37	24	7	0.86
3	5	1.07	3	7	0.43	25	2	0.85
4	8	0.90	4	2	0.45	26	3	0.85
5	8	1.00	5	2	0.55	27	7	0.85
6	11	0.86	6	5	0.57	28	5	0.81
7	8	1.06	7	4	0.60	29	5	0.86
8	8	1.13	8	9	0.58	30	2	0.86
9	6	1.14	9	5	0.57	31	28	0.88
10	10	0.97	10	5	0.59	32	5	0.91
11	5	0.95	11	18	0.61	33	9	0.93
12	9	1.01	12	19	0.64	34	11	0.93
13	6	0.78	13	10	0.65	35	7	0.97
14	7	1.04	14	4	0.61	36	3	0.95
15	6	1.08	15	3	0.68	37	5	0.93
16	7	0.89	16	2	0.69	38	5	0.98
			17	5	0.76	39	10	1.50
Average.....		0.98	18	11	0.77	40	26	1.03
			19	2	0.81	41	6	1.01
			20	4	0.81	42	3	1.05
			21	6	0.82	43	9	1.04
			22	11	0.84	44	7	1.07
			Average.....					0.78

be operating constantly in the sense that if the kidneys make the ammonia and the ammonia is essential for the regulation of the body neutrality, there will be, in the absence of nephritis, a definite amount of ammonia formed per liter of total acid produced, regardless of the total quantity per day.

Data were collected to test this assumption. For normal persons and nephritic persons Henderson's and Palmer's [7] data were taken for the daily excretion of total acid and ammonia. For diabetic patients, over 100 unselected cases were taken in order that a real value could be attached to a statistical consideration of the results. The statistics for

7. Henderson, L. J., and Palmer, W. W.: J. Biol. Chem. **17**:305, 1914; **21**:37, 1915.

TABLE 2.—*Urinary Ammonia in Persons with Diabetes Mellitus with No Albuminuria and No Ketosis*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
2867	3	0.90	3515	2	0.87
4158	2	0.97	2004	1	1.00
5831	7	1.34	977	1	0.95
274	6	0.97	844	11	0.93
5135	8	1.10	892	6	0.97
5913	7	1.06	4126	5	0.85
6109	7	0.87	2846	8	0.83
527	1	0.91	1154	3	1.05
818	6	1.07	5629	5	1.01
2783	1	1.20	456	7	0.99
2070	1	0.98	2302	7	0.86
6068	3	0.86	2601	5	0.88
6155	3	1.10	2673	5	0.83
3062	3	0.84	1604	1	0.81
3593	6	1.01	2682	1	0.86
2983	6	1.28	3531	3	0.84
1438	2	0.78	3283	4	0.81
Average					0.96

TABLE 3.—*Urinary Ammonia in Persons with Diabetes Mellitus and Ketosis with No Albuminuria*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
3503	19	1.41	818	2	0.79
274	1	1.32	844	4	1.02
1157	4	1.04	1481	10	1.07
2867	6	1.12	3470	9	1.09
3002	14	1.06	892	8	0.93
527	18	1.08	2846	2	0.96
5831	10	1.78	1154	6	1.01
4691	10	1.13	2601	15	1.12
4158	12	1.05	2002	4	0.73
1438	7	0.90	2597	15	1.29
4995	18	1.29	4487	1	1.26
5157	10	1.22	1592	7	1.12
6068	4	0.80	6100	9	1.17
6155	13	1.18	3561	5	0.83
807	20	1.13	3593	11	1.29
2783	9	1.13	2864	1	1.07
Average					1.09

TABLE 4.—*Urinary Ammonia in Persons with Diabetes Mellitus with Albuminuria but No Ketosis*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
498	7	0.77	5500	7	0.77
1193	5	0.66	5908	9	0.74
1157	8	0.76	1402	10	0.62
1213	11	0.67	783	5	0.86
1489	10	0.84	2951	5	0.55
1749	1	0.74	2968	2	0.90
3352	7	0.84	2602	3	0.81
479	8	0.77	940	9	0.55
3844	4	0.73	3501	7	0.76
3889	7	0.86	2423	4	0.66
57	1	0.69	2917	4	0.77
352	9	0.68	679	10	0.69
	1	0.77	2302	4	0.75
1739	2	0.59	5649	1	0.50
1753	8	0.71	3663	7	0.83
2380	6	0.61	2065	5	0.63
2455	13	1.03	1522	4	0.66
2365	25	0.84	2284	10	0.77
479	6	0.80	1022	4	1.09
4102	1	0.94	6136	4	1.00
4172	11	0.93	3006	3	0.74
3075	9	0.85	5961	10	0.61
3614	6	1.05	6397	4	1.04
	Average				0.75

TABLE 5.—*Urinary Ammonia in Persons with Diabetes Mellitus with Albuminuria and Ketosis*

Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid	Hospital Number	Number of Determinations	Ammonia, Grams per Liter Acid
1022	3	1.14	2951	4	0.66
1198	1	0.59	2602	15	0.93
1213	1	0.58	2423	4	0.72
1157	1	0.74	1255	6	0.71
1489	1	0.89	1207	13	0.87
6232	13	0.84	4559	6	0.55
479	1	0.82	1200	5	0.67
57	6	0.99	1040	6	0.81
2365	4	0.86	2302	5	0.83
1739	11	0.96	5649	14	0.98
1753	1	0.68	2070	3	0.72
498	2	0.96	2284	10	0.81
4102	5	0.90	6297	7	1.05
3006	2	0.51	3501	5	0.88
6136	3	0.66	1837	18	1.08
3455	10	0.99	2968	3	1.05
3655	12	0.88	3401	21	0.89
2994	7	0.82	6421	15	1.31
2682	13	0.94			
	Average				0.84

normal persons represent 122 observations in sixteen subjects. Those for nephritic persons represent 311 observations in forty-four subjects, and those for diabetic persons represent 989 observations in 112 subjects. Excretion of urinary ammonia in terms of grams per liter of total acid (titratable acid plus ammonia) excreted is recorded. Thus in recalculating the values of Henderson and Palmer's work the cubic centimeter of ammonia was multiplied by the common factor 0.0017, the value of 1 c.c. tenth normal ammonia in grams.

RESULTS

Table 1, in which the data of normal and nephritic persons are recorded, strikingly demonstrates that the production of ammonia per liter of acid excreted is greater in normal than in nephritic persons. In normal persons, the formation of ammonia is approximately 1 gm. per liter of total acid, whereas in nephritic persons it may be much less. Although diabetic persons can hardly be regarded as normal, from the point of view of the presence or absence of renal lesions, it will be noted in Table 2 that in diabetic patients with no renal lesions the response of ammonia formation to acid production closely approximates the normal values found in Henderson and Palmer's case, the averages being 0.98 and 0.96 gm. of ammonia per liter, respectively. In the case of diabetic patients with ketosis and no nephritis (Table 3), the response of ammonia formation differs little from that of diabetic patients without ketosis, the average being slightly increased, 1.09 gm. per liter. An observation made was that though the average for all values differs slightly in different persons, the different values found daily differ still less in the same person. In Tables 4 and 5, in which are recorded the data of diabetic persons with renal lesions, the average values are lower than in diabetic persons without renal lesions. It is apparent that some individual averages will resemble those of normal persons, since it has been frequently demonstrated that anatomic and functional integrity are not synonymous terms so far as nephritis is concerned. In spite of these normal values in isolated cases, the average is lower than in normal persons. An immediate clinical value may be attached to these data. The general clinical experience is that diabetic persons with nephritis are more susceptible to an acidosis than those with no nephritis, assuming other conditions, obesity, etc., as being constant. This in a great part is attributed to the vulnerability of the kidneys. The value of the estimation of the titratable acid plus ammonia and the grams of ammonia per liter of acid thus becomes enhanced. If the previously published data concerning the correlated values of blood and urine ammonia are considered, those recorded here further strengthen the view that the kidneys are the site of the formation of the urinary ammonia.

COMPARATIVE RESULTS OF COLLOIDAL GOLD AND COLLOIDAL MASTIC TESTS

AN ANALYSIS OF ONE THOUSAND SEVEN HUNDRED AND SEVEN SPINAL FLUIDS *

HARRY WASSERMANN, M.D.

BALTIMORE

It is now generally accepted that the physician who undertakes to treat syphilis is failing in his duty to the patient if he neglects routine studies of the spinal fluid. Studies carried out in this clinic [1] and elsewhere have shown that in addition to the procedures of cell count, globulin estimation and Wassermann reaction, there should be included the performance of a colloidal test such as the colloidal gold test of Lange which yields much information of diagnostic and possibly of prognostic import. Unfortunately, the preparation of the colloidal gold solution is so complex,[2] demanding absolute chemical cleanliness of all glassware and the use of triply distilled water, and the solution when prepared is so unstable that the use of this test is practically confined to large laboratories in centers of population.

Recent studies have shown that results analogous to those of the gold test may be obtained with colloidal suspensions of various gums or resins. Two of these have received particular attention, the colloidal benzoin reaction [3] in France and the colloidal mastic test in Germany [4] and in this country. In 1921, a paper was published from this clinic [5] in which the results of the colloidal mastic reaction were compared with those of the colloidal gold test in 311 fluids. It was shown that there was fairly close parallelism between the two tests and that when agreement was lacking, the mastic seemed to be somewhat more delicate than the gold.

In view of the simplicity of preparation of the reagents used in the mastic test, it has seemed worth while to review our further results with

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1. Moore, J. E.: Studies in Asymptomatic Neurosyphilis II, Bull. Johns Hopkins Hosp. **33**:231, 1922.

2. Felton, L. D.: A Study of the Specificity of the Colloidal Gold Reaction from a Physico-Chemical Standpoint, Trans. Sect. Path. & Physiol. A. M. A., 1917, p. 73.

3. Guillain, G.; Laroche, G., and Lechelle, P.: La reaction du Benzoin colloidal et les reactions colloidales du liquide cephalorachidien, Paris, Masson et Cie, 1922.

4. Kafka, V.: Mastic Reaction in Cerebrospinal Fluid, Klin. Wchnschr. **2**: 829 (April) 1923.

5. Keidel, A., and Moore, J. E.: Comparative Results of Colloidal Mastic and Colloidal Gold Tests, Arch. Neurol. & Psychiat. **6**:163 (Aug.) 1921.

it in comparison with the gold test. This paper therefore sums up the results of the study of 1,707 spinal fluids in which both colloidal tests as well as the others enumerated were performed. This series includes the 311 cases published in our first paper.[5] For the most part, the fluids are from patients in the various stages of syphilis although a number of other neurologic conditions are included. The results of spinal fluid examinations have in each instance been compared with the clinical evidence of central nervous system disease, in an attempt to evaluate the comparative worth of gold and mastic reactions.

TECHNIC

For the sake of completeness, the technic employed, which is that recommended by Stanton,[6] is repeated:

Ten grams of commercial gum mastic are dissolved in 100 c.c. of absolute alcohol, and the resultant cloudy fluid is filtered several times until a clear straw colored solution is obtained. This stock solution is

TABLE 1.—*Showing the Standards Employed in Reading the Colloidal Mastic Test, with Examples of Typical Curves* *

Examples of Colloidal Tests

	Tube									
	1	2	3	4	5	6	7	8	9	10
Dilutions of spinal fluid	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	1:2048
Paretic zone	5	5	5	5	5	4	3	2	1	0
Syphilitic zone	0	1	1	2	3	3	1	0	0	0
Mastic "3"	3	3	2	1	0	0	0	0	0	0
Negative	2	2	1	0	0	0	0	0	0	0

* 0 indicates opalescence, no change; 1, milky fluid with no precipitation; 2, milky fluid with slight precipitation; 3, milky fluid with moderate precipitation; 4, cloudy fluid with almost complete precipitation; 5, clear fluid with complete precipitation.

kept in glass stoppered bottles at room temperature and does not deteriorate on standing. The emulsion is prepared with 1 c.c. of the stock solution added to 9 c.c. of absolute alcohol, which is then added, with gentle mixing, to 40 c.c. of once distilled water.

In setting up the test, ten small tubes are employed. To the first tube in the series are added 1.5 c.c. of a stock salt solution (99 c.c. of 1.25 per cent. sodium chlorid solution plus 1 c.c. of 0.5 per cent. potassium carbonate solution), and to each of the remaining tubes 1 c.c. is added. In the first tube, there is placed 0.5 c.c. of the spinal fluid to be tested. After mixing this dilution of spinal fluid, a titration is made throughout the series by transferring 1 c.c. from the first to the second tube, from the second to the third, etc., 1 c.c. being finally discarded from the last tube. Finally, 1 c.c. of the mastic emulsion is added to each tube. After mixing, the tubes are allowed to stand over night at room temperature,

6. Stanton, J. M.: Concerning the Colloidal Mastic Test, Arch. Neurol. & Psychiat. **4**:301 (Sept.) 1920.

and the results are read in the morning. No special precautions regarding absolute cleanliness of glassware, such as are necessary for the gold test, need be observed.

The standards employed for reading results and typical readings of various types of abnormal fluids are shown in Table 1.

RESULTS

The comparative results of mastic and gold tests are summed up in Table 2. In 1,498 spinal fluids, or 87.7 per cent. of the total number studied, there was agreement between the two tests. Both were negative in 1,260 fluids, while in 238 instances both were positive, in the majority of these cases the type of curve being the same. In only 12.3 per cent. (209 cases) of the 1,707 fluids studied was there complete dis-

TABLE 2.—*A Summary of the Agreement Between Colloidal Gold and Mastic Tests, with an Analysis of Clinical and Laboratory Factors in Instances of Disagreement, Showing the Greater Delicacy of the Mastic Test*

Complete agreement (positive and negative)	1,446
Partial agreement (degrees of positive)	52
Total	1,498
Disagreement (positive and negative)	209

Analysis of the 209 in Which Disagreement Occurred

	Total Cases	Diagnosis of Neurosyphilis Supported by: Clinical Evidence	Diagnosis of Neurosyphilis Supported by: Other Spinal Fluid Abnormalities
Gold positive; mastic negative	52	16 cases or 31%	22 cases or 42%
Mastic positive; gold negative	157	75 cases or 48%	97 cases or 62%

agreement between the two tests. This group includes 157 fluids which gave positive mastic curves when the gold was negative and fifty-two in which the reverse was true. It is further apparent from Table 2 that the clinical evidence and other abnormalities in the spinal fluid tend to confirm the value of the mastic test when disagreement between it and the gold test exists.

In Table 3 these results are subjected to closer analysis. It will be noted that the only type of abnormal curve common to the two tests is the paretic curve present in 161 fluids. In fifty-two instances the gold gave a syphilitic zone or paretic zone curve when the mastic test was negative; but this is more than counterbalanced by sixty-seven instances in which the mastic test gave a paretic curve while the gold was negative. Of the total number of fluids, 1,432 were obtained from syphilitic patients, either with or without clinical evidence of nervous system damage; and 275 were obtained from patients with other neurologic diseases in most of whom puncture was performed to rule

out neurosyphilis. As shown in the table, one or both colloidal tests gave abnormal results in twenty clinically nonsyphilitic patients. These include six patients with multiple sclerosis, five with epidemic (lethargic) encephalitis and three with brain or cord tumors, while the remainder comprise various neurologic disorders. The tendency of the three diseases named to show abnormal colloidal curves is well known.

In the first paper from this clinic, it was shown that a syphilitic zone mastic curve was uncommon, and some stress was laid on the probably equivalent value of the so-called "mastic 3" curve. It is of

TABLE 3.—*Detailed Analysis of Agreement and Disagreement Between Colloidal Mastic and Colloidal Gold Curves*

Colloidal Tests	Total Cases	Diagnosis of Syphilis Without Clinical Evidence of Neurosyphilis	Diagnosis of Neurosyphilis Before Spinal Puncture	Cases for Diagnosis	Clinically Nonsyphilitic
Gold and mastic both negative	1,260	879	132	67	182
Gold and mastic both paretic	168	25	138	0	5
Gold paretic; mastic negative	18	9	9	0	0
Gold syphilitic; mastic negative	34	22	7	2	3
Gold syphilitic; mastic paretic	36	9	26	0	1
Gold negative; mastic paretic	67	23	40	0	4
Gold various; mastic "3"	117	64	44	4	5
Gold various; mastic syphilitic	7	3	2	0	2
Totals	1,707	1,034	398	73	202

TABLE 4.—*Showing the Incidence of the Paretic Type of Colloidal Gold and Mastic Curves in Various Neurosyphilitic Diseases Before Treatment*

		Gold				Mastic			
Type of Neurosyphilis	Total Cases	Paretic	Syphilitic Zone	Negative	Percentage Paretic	Paretic	Syphilitic Zone	Negative	Percentage Paretic
Paresis	44	38	2	4	86.3	40	..	1	90.9
Tabes	50	39	5	16	58.0	35	..	9	70.0
Cerebrospinal syphilis	100	34	7	59	34.0	53	..	10	53.0
Total	194	101	14	79	52.0	128	..	20	65.9

interest, therefore, to subject to further analysis the 117 instances (Table 3) of this type of curve. An impression diagnosis of neurosyphilis was made before puncture in forty-four, or 37 per cent., of these cases. The gold test was abnormal in twenty-seven (syphilitic zone 14, paretic zone 13) and negative in ninety instances. In an additional sixteen fluids (forty-three in all), there were present other spinal fluid abnormalities, usually a positive Wassermann test, to corroborate the mastic 3 curve. However, since this curve was the only abnormality present in seventy-three patients, its import still remains doubtful, and it should be interpreted only in the light of clinical evidence and other changes in the spinal fluid.

As a paretic type of curve has been found so much more frequently with the mastic than with the gold test in this series, its prognostic import as an indication of paresis is of less value than that of the gold test. Of the 395 positive mastic curves, 271 were of the paretic type; while of 283 positive gold curves, 199 were paretic. An impression still prevails among many physicians that a paretic gold curve always means paresis, present or likely to develop in the future. This type of colloidal curve is, however, fairly common in other neurosyphilitic diseases than paresis. In Table 4, this fact is amply illustrated. From this evidence the conclusion is permissible that the paretic type of colloidal test is so frequently present in tabes and diffuse cerebrospinal syphilis as to render it valueless as pathognomonic evidence of paretic neurosyphilis. This conclusion is supported by the fact that neurosyphilitic patients with paretic colloidal curves have been followed for years without the slightest evidence of mental damage. Obviously, therefore, the paretic mastic curve is less reliable than the gold as an indication of paresis, since it occurs with greater frequency in other types of neurosyphilis.

SUMMARY AND CONCLUSION

One thousand, seven hundred and seven spinal fluids have been studied to determine the comparative values of the colloidal mastic and colloidal gold tests. All other evidence, both clinical and serologic, was utilized in the analysis. It was found that in 1,498 fluids, or 87.7 per cent., there was agreement between the two tests. There was disagreement in 209, or 12.3 per cent., and in these cases the mastic test was more often positive than the gold. Clinical evidence and other spinal fluid changes tend to support a positive mastic test in spite of a negative gold test. It is pointed out that a "mastic 3" curve is of doubtful import and must be interpreted in connection with clinical and other serologic evidence. Excluding multiple sclerosis and epidemic encephalitis, abnormal colloidal curves, either gold or mastic, are practically pathognomonic of neurosyphilis. However, a paretic type of colloidal curve, although almost constant in paresis, is not necessarily indicative of that disease, since it may occur in other neurosyphilitic diseases. A paretic mastic curve is of less diagnostic or prognostic import than a paretic gold curve.

The mastic test is recommended for adoption as an integral part of spinal fluid studies partly because the simplicity of preparation of the reagents and their stability and the ease of performance of the test render it suitable for small laboratories lacking facilities for the more elaborate colloidal gold test, and partly because its delicacy is equal to or slightly greater than that of the gold test.

BOOK REVIEWS

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN. Price $8. Philadelphia: Lea and Febiger, Third edition, 1923.

Only seven years ago, Joslin wrote the first edition of his "Treatment of Diabetes Mellitus," a book of 440 pages, based on a study of 1,000 cases. The third edition is based on a study of 3,000 cases, and contains 784 pages. Dedicated "to Banting and Best and the Toronto group of insulin workers," it plunges at once into the midst of things diabetic with a 100 page discussion of insulin. The reading of these first pages in as interesting as romance, and highly instructive as showing the remarkable potency of the new therapeutic agent. The fast accumulating literature is digested and discussed, and here, as through the rest of the book, Joslin's faculty of adopting everything good for his diabetic patients is exhibited. Although the story of insulin is still too new to permit final conclusions, the reviewer is impressed with the careful and painstaking manner in which Joslin expresses his conclusions at the present time.

The dietary treatment of the disease is in the throes of controversy between the adherents of various methods of feeding. In this book, Joslin takes a broad stand, utilizing for his own treatment the best he can find in the observations and publications of his colleagues. He believes in the value of undernutrition to render the diabetic aglycosuric. The carbohydrate ration of the severe diabetic is what he can tolerate. Protein should be between 0.33 gm. and 1 gm. per kilogram of body weight. He accepts the principle that the actual quantity of food which the diabetic metabolizes is different from the actual quantity he consumes. "The caloric intake of the diabetic has been raised 31 per cent. over that of the period ending in 1917."

Throughout these pages, one finds a philosophic attitude toward all that is new in the disease and a practical appreciation of all that is old and proved.

PULMONARY TUBERCULOSIS. By MAURICE FISHBERG, M.D., Clinical Professor of Medicine, University and Bellevue Medical College; Chief of the Tuberculosis Service, Montefiore Hospital, New York City. Third edition, revised and enlarged. Cloth. Pp. 891, illustrated with 129 engravings and 28 plates. Price $8.50. Philadelphia: Lea and Febiger, 1922.

This edition, the third, has been completely revised and enlarged. The publishers reset the entire book, thereby affording opportunity for the radical changes that have been made. Two new chapters have been introduced: one on the reciprocal relations between pulmonary tuberculosis and certain physiologic and pathologic processes, the other on the medicolegal and insurance aspects of tuberculosis.

This work has undoubtedly been the best "single volume text" in English on pulmonary tuberculosis, and the present edition only serves to make its position more tenable. It is clearly written and well arranged for easy reference; all cardinal points are italicized; due credit is given for the work of others, and accurate references to the literature are appended. There are many new illustrations in this edition, in addition to those used in former editions, and they are all printed on good paper, making them clear and useful.

There is no chapter on the subject of occupational therapy in the treatment of tuberculosis, the author practically dismissing the subject with the statement: "A patient during the active course of phthisis in any stage should have no occupation at all. He cannot work, he must not attend to any vocation which requires physical or mental exertion."

This book is one of the best for use as a text for students, or for reference for the busy practitioner.